# BRAIN

## A JOURNAL OF NEUROLOGY

XUM

MACMILLAN AND CO., LIMITED
LONDON - BOMBAY - CALCUTTA - MADRAS
MELBOURNE

ST. MARTIN'S PRESS, INC.
103 PARK AVENUE, NEW YORK 17

THE MACMILLAN CO. OF CANADA LTD.
TORONTO

# Brain

## A Journal of Neurology

EDITOR

SIR RUSSELL BRAIN, D.M.

ASSISTANT EDITOR

DENIS WILLIAMS, M.D.

WITH THE HELP OF

SIR WILFRID LE GROS CLARK, D.Sc., F.R.S.
J. N. CUMINGS, M.D.
AUBREY LEWIS, M.D.
D. W. C. NORTHFIELD, F.R.C.S.
DOROTHY S. RUSSELL, M.D.
D. WHITTERIDGE, D.M., F.R.S.
O. L. ZANGWILL, M.A.

*Hon. Secretary and Treasurer to the Guarantors:*
S. NEVIN, M.D.

VOLUME LXXX

MACMILLAN AND CO., LIMITED
ST. MARTIN'S STREET, LONDON

★ ★ ★

ST. MARTIN'S PRESS, INC.
103 PARK AVENUE, NEW YORK 17

1957

XUM

# CONTENTS


| | PAGE |
|---|---|
| Hemichorea (Hemiballismus) Without Lesions in the Corpus Luysii. J. Purdon Martin | 1 |
| Developmental Abnormalities in the Region of the Foramen Magnum. John D. Spillane, Christopher Pallis and Arthur M. Jones | 11 |
| Vascular Mechanisms of Birth Injury. R. M. Norman, H. Urich and W. H. McMenemey | 49 |
| Behçet's Syndrome with Neurological Complications. Noshir Wadia and Eirian Williams | 59 |
| Vivid Day-dreaming: An Unusual Form of Confusion Following Anterior Cingulectomy. C. W. M. Whitty and W. Lewin | 72 |
| The Effects of Some Drugs on the Electrical Activity of the Brain. P. B. Bradley and J. Elkes | 77 |
| On the Nature of Pain. William Gooddy | 118 |
| Unilateral Exophthalmos. A Consideration of Symptom Pathogenesis. J. M. Van Buren, J. L. Poppen and G. Horrax | 139 |
| Changes in the Nervous System in Acute Porphyria. Raymond Hierons | 176 |
| The Incidence of Ammon's Horn Sclerosis. J. A. N. Corsellis | 193 |
| Necrotizing Encephalitis. Agatha R. Crawford and F. Lenore J. Robinson | 209 |
| An Investigation of Sound Localization in Patients with Neurological Abnormalities. E. Geoffrey Walsh | 222 |
| The Conditioned Inhibition of Uncinate Fits. Robert Efron | 251 |
| Observations on the Topography of the Lateral Column of the Human Cervical Cord. Marion C. Smith | 263 |
| Corticofugal Fibres to the Nuclei of the Dorsal Columns. An Experimental Study in the Cat. Fred Walberg | 273 |
| Rathke-Pouch Tumours. D. W. C. Northfield | 293 |
| Symmetrical Calcification of the Basal Ganglia with Familial Ataxia and Pigmentary Macular Degeneration. Robert R. J. Strobos, Ernesto de la Torre and James F. Martin | 313 |
| Arthrogryposis Multiplex due to Congenital Muscular Dystrophy. Betty Q. Banker, Maurice Victor and Raymond D. Adams | 319 |
| A Further Study of Visual-Spatial Agnosia. George Ettlinger, Elizabeth Warrington and O. L. Zangwill | 335 |
| The Phosphorus Metabolism of Gliomas: A Study with Radioactive Isotopes. Bertram Selverstone and Mildred Jewett Moulton | 362 |
| Is There a Pyramidal Tract? Paul C. Bucy | 376 |
| Brain Mechanisms and Logic. J. R. Smythies | 393 |
| Sir Charles Sherrington, Poet and Philosopher. Wilder Penfield | 402 |


U OF M BINDERY JUN 29 '58 (B)

XUM

CONTENTS


| | PAGE |
|---|---|
| Bilateral Loss of Vision from Cerebral Infarction. Sir Charles Symonds and Ian Mackenzie .. .. .. .. .. .. .. .. .. | 415 |
| The Association of Cervical Spondylosis and Disseminated Sclerosis. Sir Russell Brain and Marcia Wilkinson .. .. .. .. .. .. | 456 |
| The Appearance of the Aqueduct and Its Relationship to Hydrocephalus in the Arnold-Chiari Malformation. A. MacFarlane and A. F. J. Maloney .. | 479 |
| Intracranial Bruits in Health and Disease. N. H. Wadia and G. Monckton .. | 492 |
| The Brain-stem Conceived as the "Highest Level" of Function in the Nervous System; with Particular Reference to the "Automatic Apparatus" of Carpenter (1850) and to the "Centrencephalic Integrating System" of Penfield. Sir Francis Walshe .. .. .. .. .. .. .. | 510 |
| Sarcoidosis of the Nervous System. Michael Jefferson .. .. .. .. | 540 |
| Serum Aldolase and the Diagnosis of Myopathy. J. H. Evans and R. W. R. Baker .. .. .. .. .. .. .. .. .. .. | 557 |
| The Cervical Spine. An Anatomico-pathological Study of 70 Specimens (using a Special Technique) with Particular Reference to the Problem of Cervical Spondylosis. Eric E. Payne and John D. Spillane .. .. .. .. | 571 |
| Do the Motor Nuclei of the Cranial Nerves Receive Corticofugal Fibres? An Experimental Study in the Cat. Fred Walberg .. .. .. .. | 597 |
| Termination of the Central Pain Pathway in Man: The Conscious Appreciation of Pain. David Bowsher .. .. .. .. .. .. .. | 606 |
| Notices of Recent Publications .. .. .. .. .. 132, 288, 411, | 623 |


XUM

MARCH 1957

# BRAIN

VOL. 80, PART 1.

## HEMICHOREA (HEMIBALLISMUS) WITHOUT LESIONS IN THE CORPUS LUYSII

BY

J. PURDON MARTIN

*(From the National Hospital, Queen Square, W.C.1)*

BY 1940 the association of hemichorea—often peculiarly violent—with lesions of the corpus Luysii (subthalamic nucleus) of the opposite side had become widely recognized as a consequence of clinico-pathological observations. The cases up to 1952 have been collected and recorded by Martinez (1953). She and many other writers use the term hemiballismus instead of hemichorea, but no clear difference of meaning between the two terms has emerged. In 1948–50 Whittier and Mettler (1949 *a* and *b*), and then Carpenter, Whittier and Mettler (1950), in an extensive series of experiments on monkeys, confirmed that persistent "choreoid hyperkinesia" of the contralateral limbs regularly resulted from an isolated lesion of the corpus Luysii, provided at least 20 per cent of the volume of the nucleus was destroyed. The constancy of this association may thus be regarded as established.

From time to time, however, cases have been recorded in the literature in which the patient had suffered from hemichorea during life, but post mortem the corpus Luysii was found undamaged. Moreover, among the experimental animals of Whittier and Mettler and of Carpenter, Whittier and Mettler in which hemichorea was produced by focal lesions there were three in which the relevant corpus Luysii was found intact. It is evident therefore that it is not necessary that the corpus Luysii itself should be anatomically affected in order that hemichorea may occur.

Such "atypical" cases are worthy of special study since they are obviously capable of enlarging our knowledge of the pathology and pathogenesis of chorea, and it is to be hoped that more descriptions of them will be published. Through the kindness of colleagues I have been able to examine the pathological material of three such cases.

Any consideration of hemichorea at the present time is bound to be dominated by the experimental work of Mettler and his associates which forms much the most important physiological contribution to the subject,



XUM

and pathological findings of clinical cases must be considered in the light of their results. They not only showed that an adequate isolated lesion of the corpus Luysii was consistently followed by hemichorea of the opposite side, but they also demonstrated the importance of the globus pallidus for the abnormal movements. Whittier and Mettler, and afterwards Carpenter, Whittier and Mettler, showed that when "choreoid hyperkinesia" was already established the abnormal movements might be abolished by destruction of this nucleus or of its efferent fibres. They inferred, therefore, that the occurrence of the movements resulted from the loss of a control or co-ordinating influence normally exercised by the corpus Luysii on the pallidum, and, while this loss might be a consequence of a lesion of the corpus Luysii itself, it seemed that it might also result from a lesion interrupting the fibres connecting the body of Luys with the pallidum.

The corpus Luysii and the pallidum are connected by a to-and-fro fibre system, some of the fibres of which pass across the posterior limb of the internal capsule to (and from) the medial border of the pallidum, while others curve round its anterior margin in the ansa lenticularis, and pass upward and laterally to the anterior surface of the pallidum and the medullary laminæ. The known efferent fibres from the pallidum are contained in a bundle—the fasciculus lenticularis—which emerges from its medial angle and from the lower part of its anterior aspect and passing medially in the lower part of the ansa curves round the anterior margin of the corpus Luysii. Part of this bundle passes towards the thalamus, and part crosses to the other side of the brain. (It may, however, be questioned whether the fasciculus lenticularis contains the whole outflow from the pallidum.) Carpenter, Whittier and Mettler (1950) found that the interruption of the fasciculus lenticularis in the monkey greatly reduced an established "choreoid hyperkinesia."

*Case* I.—The clinical history was as follows: M. A. M., a woman aged 80, was admitted to the Barncoose Hospital, Redruth, Cornwall, on August 4, 1950, having had a stroke one week previously. As she was very deaf it was difficult to have any detailed communication with her. She had evident right-sided hemiplegia with the right leg lying flaccid in a position of external rotation. In the succeeding three months there was a "fair" return of power in the right arm and leg. At the beginning of November, following an attack of pneumonia, she began to have involuntary movements of her right arm and leg: they were most marked in the hand and arm and in the foot. "The hand movements were especially marked and the patient kept knocking herself against the side of her (cot) bed. The movements were choreiform in nature and although they were more severe when anyone was observing her, nevertheless they were quite bad when she was alone." She was seen by Dr. N. S. Alcock who reported the condition as "hemiballismus." It was noticed that the abnormal movements ceased during sleep and it was also observed that when the patient had another pyrexial illness the movements disappeared and recurred as she recovered. She died on January 11, 1951, five months after the onset of her hemiplegic condition and two months after the onset of her hemichorea.

*Pathology.*—The brain was examined by Dr. W. Blackwood, at the National Hospital, Queen Square. The case was one of thrombosis of the left posterior cerebral artery. The cerebral vessels generally showed well-marked, patchy atherosclerosis, and the left posterior cerebral artery was occluded by thrombus in the portion lying postero-lateral to the mid-brain. Externally the brain showed generalized gyral atrophy, with accentuation in the left occipital lobe. The atrophy of the left occipital lobe was due to an old cystic infarct which affected the pole and the postero-medial aspect of the occipital lobe, and extended on to the lateral extremity of the splenium of the corpus callosum and the lateral geniculate body. In the thalamus there was an extensive cystic infarct in the shape of a wide slit involving a large part of the body of the thalamus, including the posterior part of the lateral nucleus and the pulvinar (Plate II, fig. 1), and in the subthalamic region there was a small cystic infarct behind the corpus Luysii. There was very considerable distortion of the brain-stem, but no significant abnormality was found in it on detailed examination.

The microscopic sections (horizontal) showed that the subthalamic lesion lay behind and medial to the corpus Luysii but the corpus Luysii itself was intact (Plate I, fig. 2). There was, however, extensive degeneration of the fibres passing across the internal capsule from the posterior half of the corpus Luysii to the globus pallidus: the more anterior fibres were intact (fig. 2). More posteriorly, fibres passing across the internal capsule between the site of the subthalamic lesion and the posterior margin of the lenticular nucleus were similarly degenerated.

It seems likely that, although the tissues were not broken down, the subthalamic infarct extended along the postero-lateral margin of the corpus Luysii and was thus responsible for the degeneration of the luysii-pallidal fibres emerging from the posterior half of the nucleus. The posterior cerebral artery co-operates in the blood supply of the corpus Luysii to a variable, but usually slight, extent, the main supply being provided by the anterior choroidal and posterior communicating arteries.

A peculiar feature of this case is that no lesion was found in the motor structures to account for the right hemiplegia and we are forced to the conclusion that the hemiplegia was a sensory one, resulting from the very extensive lesion in the left thalamus. The destruction of the lateral nucleus was so severe that the patient may even have been largely unaware of her right limbs and for that reason did not move them.

I have not found in the literature any case exactly similar to this one. The old case of hemichorea described by Greiff (1883) was, however, probably one of thrombosis of the posterior cerebral artery, because there were (1) a lesion in the right occipital lobe, (2) a slit in the middle of the right thalamus, and (3) a similar slit caudal to the thalamus destroying the body of Luys: there was also (4) a small hæmorrhage in the centre of the left cerebellar hemisphere. In the case of Lloyd and Winkelman (1925) part of the hæmorrhage extended by a narrow band medially across the internal capsule and "impinged on the corpus Luysii," spreading along its lateral border; fibre degeneration is not shown but obviously in that case also many of the fibres traversing the internal capsule would have been interrupted.

Among the experimental animals of Whittier and Mettler in which

XUM

"choreoid hyperkinesia" was produced there were three in which the corpus Luysii was found intact, and in two of these animals the lesions were in the internal capsule and interrupted the subthalamo-pallidal fibres.

The pathological findings in Case I are therefore in keeping with the experimental cases of Whittier and Mettler, and are susceptible of the interpretation they propounded viz. that the hemichorea resulted because the globus pallidus was to a considerable extent isolated from a control exerted by the corpus Luysii.

*Case* II.—E. S. (3792), a woman of 68, was admitted to the National Hospital, Queen Square, on December 6, 1946, under the care of Dr. Arnold Carmichael, with the complaint of involuntary movements of the left arm and leg, of about three weeks' duration. Prior to the onset of the involuntary movements there had been a marked decline in the patient's mental and physical activity over a period of two months or more. The involuntary movements had come on gradually, and had increased before her admission. The movements observed in hospital were typically choreic and included large movements throwing the arm out from the shoulder or the leg from the hip; the muscles of the left side of the neck were involved in the movements causing rotation and deviation of the head and there were grimacing movements of the left half of the face. The movements ceased during sleep and might cease for a minute or so at a time while the patient was awake. Five days after the patient's admission the movements ceased, and there was some loss of power in the limbs of the left side, most pronounced in the hand. A week later there was a slight return of the movements, but after another two weeks the hemiparesis increased with complete abolition of the movements, and the patient's condition gradually deteriorated. She died five weeks after her admission to the hospital and approximately two months after the onset of her hemichorea, and one month after the first signs of hemiparesis.

*Pathology.*—Naked-eye examination of the brain revealed no abnormality. More detailed examination after fixation showed areas of softening in the central region on both sides, and the central portions of the brain were submitted to serial microscopic examination. The subthalamic nuclei (corpus Luysii) on both sides were normal. On the right side there was a recent lesion in the medial portion of the globus pallidus, extending into the internal capsule (fig. 3) and this was regarded as the cause of the final left hemiparesis, and abolition of the hemichorea. There was an older lesion, associated with heavy deposits of iron-containing granules, which involved the anterior portion of the globus pallidus and extended upwards and outwards along its whole anterior margin (fig. 3), spreading into the internal capsule at the genu and into the anterior limb adjacent to the margin of the pallidum, and also into the external medullary lamina between the pallidum and the putamen. In the higher sections part of the genu and of the anterior limb of the capsule were demyelinated and partially softened. With the exception of a small portion of the putamen adjacent to the main lesion, the putamen and caudate showed no softening or cavitation. On the left side there was a small focus of softening in the anterior half of the globus pallidus with deposition of iron-containing granules around the vessels and many fat granule cells.

In short, the most recent lesion on the right side destroyed the medial portion of the globus pallidus, and so, according to the work of Carpenter, Whittier and Mettler, was perfectly placed to abolish the chorea. Prior to the occurrence of this lesion the main portion of the globus pallidus must have been relatively intact, with the older lesion surrounding its anterior surface and extending into the internal capsule on the medial

XUM

side and into the external medullary lamina on the lateral side. It was not possible to follow any individual groups of fibres but all the structures in the situation of the upper part of the ansa lenticularis were destroyed.

Of similar cases in the literature, the most important are those of Fragnito and Scarpini (1926) and of Papez, Bennett and Cash (1942).

In the case of Papez, Bennett and Cash the main lesion was in the anterior part of the outer segment of the globus pallidus, extending into the external medullary lamina and medially into the internal capsule along the anterior margin of the pallidum. The authors were able to demonstrate degeneration of fibres between the site of the lesion and the subthalamic nucleus; they considered that these were afferent to the corpus Luysii, but from the work of Whittier and Mettler it is probable that many of them were running in the opposite direction, i.e. subthalamo-pallidal. (There was also a lesion on the other side, situated anterior to the red nucleus, directly in the course of the crossing subthalamo-tegmental fibres.)

In the case of Fragnito and Scarpini the lesions lay: (1) along the anterior and medial border of the putamen and pallidum, with some lacunæ in the caudate, (2) in the body of the putamen, and (3) along the external medullary lamina and the outer margin of the pallidum. The cases of Munch-Petersen (1949) and Rothfeld-Demianowska (1937), seem, from the short descriptions, to have been similar.

These cases and our Case II have in common the presence of lesions around the anterior margin of the pallidum and in the external medullary lamina. In the present state of our knowledge it is impossible to be dogmatic about the mechanism of the choreic syndrome in such cases, but my interpretation is that the lesions interrupt a large contingent of fibres from the corpus Luysii passing in the ansa lenticularis upwards and forwards along the front of the globus pallidus to enter it either directly, from the front, or laterally by way of the external medullary lamina. Many fibres of the ansa lenticularis turn into or emerge from the medullary laminæ, and, if they are interrupted, the controlling influence of the corpus Luysii on the activity of the globus pallidus must be greatly impaired. In all these cases the lesions are too high to interrupt the efferent fibres of the pallidum in the fasciculus lenticularis.

Neither in Case II, nor in the other cases I have referred to, was the hemichorea of the same violence as is seen when the corpus Luysii itself is destroyed by a focal lesion.

It should be added that in the third animal of Whittier and Mettler in which "choreoid hyperkinesia" was present, although the corpus Luysii was intact, the lesions were situated around the globus pallidus—in the caudate, putamen, external medullary lamina and extending posteriorly into the internal capsule; the globus pallidus and its medial border whence most of its efferent fibres emerge, were largely intact, so that the findings are consistent with the suggestion that the pallidum was still active but isolated from the controlling influence of the corpus Luysii.

XUM

*Case* III.—E. B., female, 74 (No. 36501), admitted under the care of Sir Charles Symonds on February 7, 1952: she died on February 29, 1952.

For some long time she had been liable to irregular movements of the right foot and towards the end of 1951 these had extended to affect the whole limb. Early in January 1952, while shopping, she had a sudden increase of these movements and was taken home: next morning she had uncontrollable movements of the right arm as well and thereafter movements of both the limbs of the right side persisted. She also had occasional difficulty in speaking, being unable to utter the words properly. It was noticed that the movements of her right arm and leg ceased during sleep.

In hospital there were continuous movements of the limbs of the right side while the patient was awake. The movements of the arm were of large amplitude, and those of the lower limb somewhat less. They were choreic in character. Power was good; the tendon-jerks were all present and both plantar reflexes were flexor. The patient was able to walk, controlling the movements of the right leg fairly well as she did so, while the right hand and arm moved wildly about. Her blood pressure was 210/98 mm.Hg. Her heart was moderately enlarged, with regular rhythm and no murmurs. On February 25 the patient was found dysphasic, with right hemiparesis and complete abolition of her abnormal movements: the right plantar reflex was extensor. The involuntary movements reappeared in the right arm two days later, but in a much milder form. The patient remained dysphasic and confused, and died after another two days.

*Pathology.*—The brain showed moderate gyral atrophy in the fronto-parietal areas. All the arteries at the base of the brain were very atheromatous, especially the basilar, posterior cerebral, posterior communicating, middle cerebral and internal carotid arteries. On the left side, not only was there atheromatous thickening at the origin of the internal carotid artery, but partly organized clot filled the whole of this artery up to the syphon. The circle of Willis was symmetrical.

On section of the brain, the cortex on the medial aspect of the left frontal lobe showed hæmorrhagic infarction (fig. 5), and some hæmorrhagic stippling was present in the cortex of the insula. The corpora Luysii appeared healthy, as also did the basal ganglia in general.

On microscopic examination the left carotid artery showed occlusion both by old recanalized clot and by recent clot. Longitudinal section of the carotid syphon showed that it was obstructed, principally by old organized clot which had been recanalized and also by recent clot. The hæmorrhagic infarction in the medial portion of the superior frontal gyrus was considered to be very recent, and there was a similar very recent one in the upper part of the precentral gyrus. In the middle frontal gyrus (in the distribution of the middle cerebral artery) there were several older small foci of ischæmic degeneration. There was no abnormality in the lenticular nucleus, corpus Luysii, thalamus or substantia nigra. There was marked atheroma of the posterior cerebral artery. The red nuclei, mid-brain and brain-stem generally showed no lesions: the dentate nuclei also appeared normal.

The case, was, therefore, one of thrombosis of the internal carotid artery, the whole of this artery up to and including the syphon being filled with thrombus. The openings of the anterior choroidal artery and the posterior communicating artery arising just above the syphon were not obstructed.

It will be recalled that these are the arteries which provide the main blood supply to the corpus Luysii. In the circumstances the branch of the

posterior communicating artery passing up to the corpus Luysii was dependent solely on the circulation from the posterior cerebral connexion of the posterior communicating artery, and, what is probably more important, the anterior choroidal supply was entirely dependent on the flow through the posterior communicating artery. The total blood supply to the corpus Luysii must therefore have been greatly diminished and especially the supply by way of the anterior choroidal artery. In addition, the posterior cerebral artery, which provides the rest of the blood supply to the corpus Luysii was markedly atheromatous.

We are dealing with a balance between the activity of the globus pallidus on the one hand and the controlling or co-ordinating influence of the corpus Luysii on the other, and so any considerable impairment of the action of the subthalamic nucleus may permit a release of irregular activity of the pallidum, with consequent hemichorea. The relative ischæmia of the corpus Luysii may therefore have been significant, provided there was not the same degree of ischæmia of the globus pallidus. The latter receives most of its blood supply from the anterior cerebral artery by way of Heubner's artery, and it receives some supply from the anterior choroidal artery. In this instance the circle of Willis was still unbroken and the left anterior cerebral artery, though its principal supply from the internal carotid was obstructed, still received blood both by way of the anterior communicating artery and by way of the posterior communicating artery and the terminal portion of the internal carotid. It is possible, therefore, that the pallidum suffered a less severe degree of ischæmia than the corpus Luysii, and was capable of relatively greater activity. According to this view the softenings in the frontal area, which lay in the peripheral distribution of the middle and anterior cerebral arteries were not significant in themselves for the occurrence of the chorea, but merely as evidence of ischæmia.

My interpretation of this case rests on the supposition that the severe impairment of the blood supply of the hemisphere affected the corpus Luysii relatively more than the pallidum, with the result that the controlling influence of the former was at times inadequate.

This introduces a factor which, as far as I know, has not been taken into account before in the discussion of cases of hemichorea (hemiballismus) and which may be of importance in other cases in which the pathological findings are anomalous, viz.: impairment of the functional activity of the corpus Luysii while it is still anatomically normal. Some years ago I saw a patient with a moderate right hemichorea of recent gradual onset; the patient died within a few weeks and was found to have a subdural hæmatoma on the right side and I was informed that this was the only cerebral abnormality discovered. Dr. Goodbody has told me of a similar case. The displacement of the brain in cases of subdural hæmatoma is so great that the circulation in the posterior cerebral artery may be severely

impaired and it is possible that this, in turn, may in some cases cause ischæmia of the corpus Luysii, and so give rise to hemichorea.

I must mention that there are in the literature two important descriptions of cases of hemichorea with lesions in the frontal lobes. In that of Macken (1949), the lesion which was regarded as significant was in the first and second frontal gyri. In the case of Tronconi (1948) there was a lesion in the third frontal gyrus, and there was also a small lesion in the thalamus and subthalamic region interrupting one of the bundles of Forel. In both cases the subthalamic nuclei (corpus Luysii) were undamaged.

## Conclusion

Mettler and his associates showed that in the monkey "choreoid hyperkinesia" occurred when the corpus Luysii was seriously damaged and the globus pallidus was intact, and we must infer that the choreic movements depend on irregular impulses issuing from the globus pallidus when the co-ordinating influence of the corpus Luysii is removed. Moreover we know from experience with human subjects that the hemichorea is of great violence when the corpus Luysii is completely destroyed and the globus pallidus undamaged. Although in each of the cases I have described here the corpus Luysii was intact, the findings do not conflict with these physiological ideas. In the first two cases, as in a few of Whittier and Mettler's animals, the lesions interrupted a considerable proportion of the connecting fibres between the corpus Luysii and the globus pallidus, thus releasing the latter to a considerable degree from the controlling influence of the former, while most of the globus pallidus and its efferent fibres were intact. The isolation of the globus pallidus from the corpus Luysii was by no means complete in either case, and the associated hemichorea had none of the extreme violence that we see with total destruction of the corpus Luysii and an intact globus pallidus. Another influence which would be likely to reduce the violence of the hemichorea in the second case, and in several of the previously described cases, is damage to the globus pallidus, and here again the observed facts are in keeping with the theory.

The third case introduces a new consideration, viz. the balance of functional capacity between the two nuclei. If it is accepted that, in the conditions of ischæmia which prevailed, the corpus Luysii was at times unable to exercise sufficient control over the globus pallidus, then this case, too, may be explained in accordance with the same physiological ideas. This conception of a reduction of the functional capacity of the corpus Luysii by ischæmia (without softening) is applicable to other cases in which hemichorea has occurred in association with pathological disturbances of different kinds, and should be borne in mind whenever in a case of hemichorea the corpus Luysii is found undamaged.

Hemichorea depends in some way on the globus pallidus being relatively

intact and so is probably due to impulses—presumably irregular impulses —issuing from the globus pallidus. This answers the first of the fundamental questions in regard to hemichorea and which were put forward by Martin and Alcock (1934), viz. Where do the abnormal impulses arise? Our present material gives us little help in addressing ourselves to the succeeding questions which may be expressed comprehensively: How are these irregular impulses projected into the motor system to produce hemichorea (hemiballismus)?

It is to be hoped that more descriptions will be published of "atypical" findings in cases of hemichorea (hemiballismus). Cases of which the interpretation is not clear in terms of our present knowledge are particularly important since they are most likely to lead to some extension of our knowledge in the future.

## Summary

Three cases are described, in each of which, following hemichorea during life, the relevant corpus Luysii was found intact post mortem.

These cases are considered in the light of the experimental results of Carpenter, Whittier and Mettler which indicate that the irregular impulses responsible for the chorea proceed from the globus pallidus and that normally a co-ordinating influence over them is exercised by (or through) the corpus Luysii; this is mediated by a to-and-fro fibre system connecting these two nuclei.

In the first case described, although the corpus Luysii was intact, many fibres connecting it with the globus pallidus were degenerated and they are believed to have been affected by a vascular lesion which bordered on the corpus Luysii.

In the second case, a group of vascular lesions along the anterior margin of the globus pallidus must have largely isolated it from the control of the corpus Luysii. A final lesion, occurring several weeks before death, abolished the chorea and had destroyed the medial part of the globus pallidus.

In the third case hemichorea on the right side was associated with obstruction of the left internal carotid artery, and with post-mortem evidence of ischæmia of parts of the left cerebral hemisphere. The suggestion is made that although the corpus Luysii was not degenerated its activity was impaired by a considerable degree of ischæmia and the globus pallidus was relatively less affected.

Among the vascular disturbances with which hemichorea may be associated are thrombosis of the posterior cerebral artery (proximal to its subthalamic branch) and thrombosis of the internal carotid artery.

I am greatly indebted to those colleagues, both clinicians and pathologists, who have so generously placed the material of their cases at my

disposal—Sir Charles Symonds, Dr. E. A. Carmichael, Dr. T. S. Wilson and Dr. J. G. Greenfield, Dr. W. Blackwood and Dr. R. Salm—and also to Dr. Greenfield and Dr. Blackwood for much technical and personal help.

## REFERENCES

CARPENTER, M. B., WHITTIER, J. R., and METTLER, F. A. (1950) *J. comp. Neurol.*, **92,** 293.
FRAGNITO, O., and SCARPINI, V. (1926) *Riv. Pat. nerv. ment.*, **31,** 524.
GREIFF, F. (1883) *Arch. Psychiat. Nervenkr.*, **14,** 598.
LLOYD, J. H., and WINKELMAN, N. W. (1925) *Amer. J. med. Sci.*, **169,** 247.
MACKEN, J. (1949) *Acta Neurol. belg.*, **49,** 909.
MARTIN, J. P., and ALCOCK, N. S. (1934) *Brain*, **57,** 504.
MARTINEZ, Y. (1953) Contribution à l'étude de l'Hémiballisme. Paris.
MUNCH-PETERSEN (1949) Fourth International Congress of Neurology, Paris, Vol. 2, p. 59.
PAPEZ, J. W., BENNETT, A. E., and CASH, P. T. (1942) *Arch. Neurol. Psychiat., Chicago*, **47,** 667.
ROTHFELD, J., and DEMIANOWSKA, M. (1937) *Zbl. ges. Neurol. Psychiat.*, **83,** 460.
TRONCONI, V. (1948) *Riv. Neurol.*, **18,** 1.
WHITTIER, J. R., and METTLER, F. A. (1949*a*) *J. comp. Neurol.*, **90,** 281.
——, —— (1949*b*) *J. comp. Neurol.*, **90,** 319.

## LEGENDS FOR PLATES

### PLATE I

FIG. 2 (*Case* 1).—Low power view of a horizontal section showing degenerated and intact fibres crossing the internal capsule. The corpus Luysii is intact. Loyez stain.

### PLATE II

FIG. 1 (*Case* 1).—The lesion in the left thalamus. (The section is reversed in the photograph.) Stain P.A.H.

FIG. 3 (*Case* 2).—Recent lesion in the lower medial portion of the globus pallidus. Stain P.A.H. ; the lesion appears dark.

FIG. 4 (*Case* 2).—Older lesion involving anterior part of the globus pallidus and medullary laminæ, and extending into the putamen and anterior limb of the internal capsule. Another lesion in the medial part of the caudate nucleus. Loyez stain; the lesions appear pale.

FIG. 5 (*Case* 3).—Softening in the medial portion of the left superior frontal gyrus.

PLATE I

FIG. 2.

*To illustrate article by J. Purdon Martin.*

XUM

PLATE II

FIG. 1.

FIG. 3.

FIG. 4.

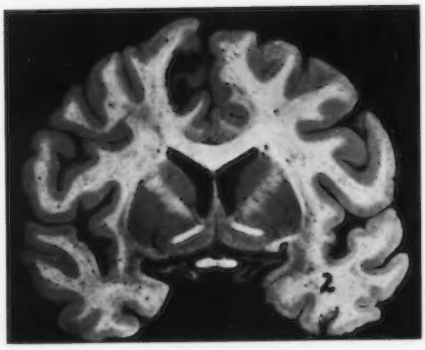

FIG. 5.

*To illustrate article by J. Purdon Martin.*

# DEVELOPMENTAL ABNORMALITIES IN THE REGION OF THE FORAMEN MAGNUM

BY

JOHN D. SPILLANE, CHRISTOPHER PALLIS AND ARTHUR M. JONES

*(From the Departments of Neurology and Radiology, United Cardiff Hospitals)*

THE nervous system is one of the most common sites of malformation. Record and McKeown (1949) found that such anomalies occurred in nearly 0·6 per cent of all notified births. Spina bifida with meningocele or meningo-myelocele, anencephalus and hydrocephalus were the commonest defects in their large series of 930 consecutive cases of neural anomalies causing stillbirth or death in the first year of life. The ætiology of such lesions is variable but defects in the germ plasm, disturbed fœtal environment from infection, toxæmia or maternal nutritional deficiency and other factors may all play a rôle. Gross lesions are incompatible with life and many others soon betray their presence, but it has been appreciated in recent years that some malformations of the nervous system or of its bony envelope, the skull and spine, may remain clinically silent until adult life is reached. Symptoms may then develop closely resembling those of acquired neurological diseases and the developmental character of the lesions may not be recognized until operation or autopsy. An understanding of the processes which initiate these late and progressive symptoms is of considerable importance.

We are here concerned with the developmental anomalies found in the region of the foramen magnum. These may be skeletal, neural or of combined type. (In the latter case it is often difficult to decide the true nature of the association.) Perhaps the most interesting feature about them is their diversity: each type may vary in degree, in its clinical effects, and in the pattern of its association with other neural or skeletal defects in the neighbourhood. For example, marked *primary basilar impression* may be found without compression of the neuraxis, intramedullary cavitation or cerebellar displacement. In other cases, a progressive upper cervical syndrome may develop in a patient with only slight basilar impression. In cases of synostosis of the atlas to the occiput (*occipitalization*) the neurological disorder is equally variable and dural bands or cerebellar displacement may be revealed at operation in addition to the more commonly found dislocation of the odontoid. In the *Klippel-Feil syndrome* (*congenital cervical synostosis*) the fusion of cervical vertebræ

XUM

may be the only defect or it may be associated with basilar impression or occipitalization of the atlas. Some of those affected may show little disability despite gross bony deformity, others may develop spastic paraplegia, syringomyelia or hydrocephalus. Cerebellar ectopia may be demonstrated in some cases. The *Arnold-Chiari malformation* and other types of displacement of the cerebellum into the spinal canal may occur with or without skeletal anomalies about the foramen magnum. Clinical manifestations may appear in infancy, childhood or adult life and may vary from a single symptom, such as oscillopsia, to gross disturbances, such as syringomyelia or cerebellar staxia.

Finally, the pathological processes found at operation to be responsible for a given syndrome may differ. Clinical syringomyelia in a patient with a skeletal anomaly at the cranio-vertebral junction may result from intramedullary cavitation (representing true syringomyelia, hydromyelia or ischæmic necrosis) or from compression of the neuraxis (by a stenosed foramen magnum, a displaced odontoid, a dural band or by cerebellar "herniation"). These various statements will be substantiated in the course of this paper.

From these preliminary remarks the clinician should not be surprised if "characteristic" or "typical" cases are not often seen, nor if certain stigmata which immediately suggest the diagnosis of an anomaly in some patients are wholly lacking in others. Each case should be dealt with on its merits.

*Nomenclature.*—We shall have to define the sense in which we use certain well-known terms, as current nomenclature in this field is often confusing. To some the "Klippel-Feil syndrome" is a clinical concept (persons with a low hair-line and a short, possibly webbed, neck) while others use the term when in a routine radiograph two or three cervical vertebræ are found to be fused, irrespective of the clinical appearance of the patient. The terms "occipitalization" and "assimilation" of the atlas are either used synonymously, or to describe varying degrees of atlanto-occipital synostosis. As for the words "platybasia" and "basilar impression," they mean very different things to different people. Lastly, as varying degrees of cerebellar displacement into the spinal canal may be found in association with cranio-vertebral anomalies we shall have to consider the classification of cerebellar ectopia and the essential features of the "Arnold-Chiari malformation."

## The Clinical Material

Our report is based on a study of 24 neurologically disabled patients with bony and/or neural anomalies of a *developmental* nature in the region of the foramen magnum. Cases of *acquired* skeletal abnormality were excluded. We also excluded cases in which the neurological disability was considered unrelated to the abnormalities at the foramen magnum.

XUM

Congenital bony defects at the cranio-vertebral junction may be harmless and unassociated with symptoms or signs. We have seen 10 such cases (not included in the series) to which we shall first briefly refer. There were 8 patients with basilar impression (of whom 4 also had other skeletal anomalies at the craniovertebral junction); 1 patient had occipitalization of the atlas and fusion of the cervical vertebræ; and another a double spina bifida of the atlas (unfused anterior and posterior arches). These various anomalies differed in degree and were found in patients of very different ages. No neurological repercussions had occurred, even when the anomaly was gross and of long duration. In several cases multiple anomalies were present, a finding which does not support the suggestion sometimes made that, whereas isolated basilar impression may be asymptomatic, its presence in conjunction with other skeletal defects is always associated with neurological signs.

With the exception of Case 23 examined by one of us (J. D. S.) in 1945, the 24 cases forming the basis of this report were seen in South Wales during the period 1947–1956.

*Age.*—There are no infants in the series: the youngest patient was aged 7 and the oldest was 64 years old when they first came under our care. Only 3 were aged less than 20—there were 8 cases in the twenties, 10 in the thirties, and 1 each in the forties, fifties and sixties respectively.

*The duration of symptoms* before the patient came under observation was as follows:

| | | |
|---|---|---|
| Less than one year | .. | 1 case |
| One to five years | .. | 9 cases |
| Six to ten years | .. | 6 cases |
| Over ten years | .. | 8 cases |

About half of these patients presented abnormal configurations of the head and neck which will be discussed further on. This unusual appearance not infrequently suggested the diagnosis. The neurological syndromes encountered were diverse and varied greatly in severity. Eight patients were operated upon.

## Radiological Abnormalities

(1) *Fusion of Cervical Vertebræ*

*Fusions were present in* 6 *patients* (*Cases* 10, 12, 13, 17, 23 and 24); they were extensive in two (23 and 24). They involved C2—C3 in four. The atlas was occipitalized in each instance. In Case 17 the odontoid was fused to the clivus (Plate VI, fig. 16).

Fusion was usually most apparent in relation to the vertebral bodies. The degree of coalescence between adjacent segments varied. In some cases there was an almost complete obliteration of the normal disc space; in others there were rudimentary disc spaces, a linear change in density

in the lateral film pointing to the site of the missing disc. The laminæ and apophyseal joints were often fused but fusion of adjacent pedicles, with obliteration of intervertebral foramina, was not encountered. The spinous processes were as often fused as separate.

We have only designated Cases 23 and 24 as instances of the "Klippel-Feil syndrome". The original patient described by Klippel and Feil (1912) had only four cervical vertebræ, fused into a single column of bone. Feil (1921) later broadened his concept of the defect to include (*a*) complete fusion of the cervical spine, (*b*) reduction in the number of cervical vertebræ and (*c*) partial coalescence of two or more cervical segments. There has been a tendency to apply the term "Klippel-Feil syndrome" to all these variants, but as Erskine (1946) pointed out, most of the cases recorded since the original description have not been of such extreme type. Few patients with these "lesser" anomalies show Feil's "essential" clinical triad of short neck, low hair-line, and limitation of neck movements. A considerable degree of fusion may be present without alteration of external configuration. One may speak of "congenital cervical synostosis," indicating its extent, and retain the eponymous term to describe patients with the "essential" clinical features and radiographic evidence of either complete fusion of the cervical spine or true reduction in the number of cervical vertebræ.

(2) *Occipitalization of the Atlas*

The term will be used to denote *any* degree of atlanto-occipital synostosis. Such synostosis may affect the anterior arch of the atlas, fusing it to the lower end of the clivus, or the posterior arch, which is then fused to the squamous occiput, just below the posterior rim of the foramen magnum. Both anterior and posterior fusions may be present in the same patient. The lateral masses moreover may be occipitalized on one or both sides or there may be synostosis at one or both atlanto-occipital joints. The term "assimilation" of the atlas is perhaps justifiable when *all* components of the vertebra are in bony continuity with the base of the skull (such complete synotosis can only be diagnosed after antero-posterior and lateral tomograms of the foramen magnum have been taken). Rather than introduce the term "assimilation" into the present discussion, however, we have preferred to speak of complete occipitalization contrasting this with occipitalization confined to the anterior or posterior arch or to one or both lateral masses.

Occipitalization of the posterior arch of the atlas can usually be diagnosed from a good lateral film, taken with the neck in full flexion, a procedure which, in normal persons, will produce maximum separation of the posterior arch from the overlying part of the squamous occiput. The anterior arch may sometimes be considered occipitalized on the plain lateral film, but the lateral tomogram may show that it is not in fact fused

XUM

to the clivus. Plain films taken through the open mouth and centred on the odontoid may suggest the presence of synostosis at the atlanto-occipital articulations but antero-posterior tomograms are required for confirmation of such fusion and in order to establish a diagnosis of occipitalization of the lateral masses.

*Seven patients had occipitalization of the atlas.* (*Cases* 10, 11, 12, 13, 17, 23 and 24.) In Cases 12 and 17 (fig. 16) the atlas was completely occipitalized. In these two cases a small spicule of bone projected from the squamous occiput in the region of the posterior rim of the foramen magnum, probably representing the remnants of the posterior arch. In Cases 10, 11, 13, 23 and 24 occipitalization was less complete. In Case 10 the anterior arch and lateral masses were free, but the posterior arch was fused to the occiput (fig. 12) and there were bilateral synostoses of the atlanto-occipital articulations. In Case 11 there was occipitalization of the anterior arch and of the left lateral mass. The posterior arch was represented by two small nodules below the squamous occiput. The right lateral mass was free (fig. 14). In Cases 13, 23 and 24 the anterior arch was free but the posterior arch was occipitalized.

Occipitalization of the atlas was frequently associated with other anomalies of the cranio-vertebral junction. The association with fusion of cervical vertebræ was particularly frequent, 6 of our 7 patients with occipitalization showing fusions at various levels of the cervical spine. 5 patients had basilar impression but only 2 had chronic atlanto-axial dislocation. This is of interest in view of the statement made by McRae and Barnum (1953) that when assimilation of the atlas is associated with neurological signs "the most significant finding . . . (is) an odontoid process of abnormal size, or in an abnormal position, or with an abnormal mobility." Atlanto-axial dislocation was found in two-thirds of their cases of occipitalized atlas with neurological complications.

(3) *Atlanto-axial Dislocation*

This denotes an abnormal mobility between atlas and axis. *Congenital* atlanto-axial dislocation may arise from congenital absence of the odontoid, from failure of the odontoid to fuse with the body of the axis or from absence or abnormal laxity of the ligament normally binding the odontoid to the anterior arch of the atlas.

The most useful projection for showing atlanto-axial dislocation is a lateral film taken with the head in full flexion. Lateral tomograms in flexion and extension were taken when necessary. *Two patients* (*Cases* 11 and 12) *in the present series showed atlanto-axial dislocation.* In both cases there were other anomalies at the cranio-vertebral junction and as there was no history of injury it was considered that the atlanto-axial dislocation was congenital in character. In each case the odontoid was

XUM

normally developed and fused to the body of the axis so that the defect was probably an insufficiency of the transverse ligament of the atlas.

McRae (1953) found that neurological signs were always present, in cases of atlanto-axial dislocation, when the antero-posterior diameter of the spinal canal, behind the odontoid, was 19 mm. or less; or when the odontoid moved back and forth more than 3 mm. on flexion and extension of the head. The antero-posterior diameter of the foramen magnum and the effective antero-posterior diameter of the spinal canal at the level of the atlas were measured on radiographs in most of our patients. The submento-vertical projection was not found satisfactory for the first of these measurements. In this view too many lines of somewhat similar shape (representing the upper vertebræ of the extended neck) are superimposed on the foramen magnum. More accurate measurements could be obtained from the lateral plain film or mid-sagittal tomogram. Readings were taken (*a*) from the anterior to the posterior lip of the foramen magnum and (*b*) from the anterior cortex of the posterior arch of the atlas to the nearest point of the posterior cortex of the odontoid. In each instance, the smaller of these two measurements was recorded.

Readings were available for 18 of the patients and ranged from 14 mm. to 45 mm. with a mean of 28 mm. and a standard deviation of 7·1 mm. In 4 patients, the antero-posterior diameters of the upper cervical canal were reduced to less than 20 mm., the measurements recorded being 19 mm. (Case 7), 17 mm. (Case 17), 16 mm. (Case 11), and 14 mm. (Case 12). Of these 4 patients only two (Cases 11 and 12) showed fairly definite evidence of compression of the spinal cord: atlanto-axial dislocation was present in both. 2 patients (Cases 7 and 18) appeared to have a primary stenosis of the atlas. McRae's (1953) observations may therefore be amplified. It would appear:

(*a*) that a narrow spinal canal ($\leqslant$19 mm. at the level of the atlas) can be found without long tract signs;

(*b*) that when atlanto-axial dislocation is the cause of such canal narrowing neurological signs often occur.

The variable repercussions of a narrow spinal canal, at the level of the atlas, could be accounted for by differences, in different patients, in the size of the enclosed cord or in the pattern of its blood supply, or by the known occurrence, in certain of these cases, of dural bands or other structural abnormalities of the soft tissues not demonstrable by radiography yet capable of causing cord compression. It is probable moreover that *intermittent* narrowing of the spinal canal, such as presumably occurs in cases of atlanto-axial dislocation, is more harmful to the cord than narrowing not liable to such repeated variations.

XUM

(4) *Platybasia and Basilar Impression*

*Platybasia* denotes an increase in the breadth (obtuseness) of the basal angle of the skull which is the angle made by the intersection of the plane of the sphenoid with the plane of the clivus. *Basilar impression* is a deformity of the base of the skull consisting in an elevation into the cranial cavity of a variable part of the bony rim of the foramen magnum.

The word "platybasia", attributed to Virchow, has been used by anthropologists interested in craniometry since the middle of the nineteenth century (Topinard, 1899). The Swedish anatomists, Berg and Retzius (1855), introduced the term "impressio baseos cranii" to denote the characteristic deformity of the rim of the foramen magnum. Boogard (1865) later showed that the basal angle could be increased in some cases of basilar impression. Pathologists (Rokitansky, 1846; Virchow, 1856, 1857), clinicians (Homen, 1901: Sicard and Oberthur, 1904) and finally a radiologist (Schuller, 1911) gave early descriptions of the effects of primary or secondary forms of basilar impression and clearly described the essential feature of invagination of the foraminal rim.

Confusion between platybasia and basilar impression seems to date from 1939. In that year Chamberlain published a paper called "Basilar impression (platybasia)—a bizarre developmental anomaly of the occipital bone and upper cervical spine with striking and misleading neurological manifestations." Chamberlain's paper had two main effects. On the one hand, it resulted in many new cases of basilar impression being recognized, some free of all symptoms, others with severe disability. A good lateral film showing the lower part of the skull and upper part of the cervical spine was all that was required. Chamberlain's "base line" (from the posterior edge of the hard palate to the posterior lip of the foramen magnum) was easy to trace, although the posterior landmark was at times difficult to identify. In many neurological clinics, when past radiographs were re-examined, cases of basilar impression were recognized where previously the diagnosis had not been suspected. The description of what came to be known as "Chamberlain's line" gave the impetus to many subsequent developments in the radiological diagnosis of this anomaly. The other effect of Chamberlain's paper, however, was to introduce the term "platybasia" into the vocabulary of the clinician. This has undoubtedly led to confusion, particularly in the writings of British and American authors. The terms platybasia and basilar impression, synonyms by implication in the title of Chamberlain's important paper, do not refer to the same anomaly. Invagination of the rim of the foramen magnum is not always associated with an increase in the basal angle of the skull: in fact, in the majority of cases of basilar impression there is no platybasia. The use of antero-posterior and lateral tomograms shows this quite clearly.

In 1941 Walsh *et al.* stated that the two conditions (basilar impression and platybasia) were not identical. Although the distinction between

the conditions is being gradually appreciated (Moreton, 1943; Edwards, 1946; McGregor, 1948; O'Connell and Turner, 1950; Garcin and Oeconomos, 1953), most modern textbooks of neurology (Elliott, Hughes and Turner, 1952; Brain, 1955; Baker, 1955; Merritt, 1955) still refer to "platybasia or basilar impression."

*The Measurement of Platybasia.*—Boogard (1865) on direct measurement, found the basal angle to vary between 103·5 degrees and 131·5 degrees. In a lateral film of the skull, the plane of the sphenoid (plane of the anterior fossa) is determined by drawing a line from the nasion (naso-frontal suture) to the tuberculum sellæ (McRae, 1953), centre of the pituitary fossa (McGregor, 1948), or posterior clinoids (List, 1941, Brailsford, 1944). The plane of the clivus is determined by drawing a line from the tuberculum sellæ, centre of the pituitary fossa or posterior clinoids to the anterior lip of the foramen magnum. Although the point of intersection of the two lines varies, the resulting variation in the basal angle does not exceed a few degrees.

List (1941) considered the normal range of the angle to be 115–140 degrees but did not mention the number of observations on which he based these figures. Walsh *et al.* (1941) gave the range as 115–150 degrees. Brailsford (1944) states the mean value of the angle to be 135 degrees and the maximum angle in normal people to be 148·5 degrees. McGregor (1948) on the basis of measurements taken from the lateral radiographs of 203 Bantu skulls gives the mean value as 134 degrees with a standard deviation of 6·44 degrees. Taking the maximum limit of normality to be the mean plus twice the standard deviation, he puts the uppermost limit of the normal basal angle at 148 degrees. Poppel *et al.* (1953) measured the angle in 102 normal persons. They found the mean value to be 136·7 degrees, with a standard error of 5·3 degrees. McRae and Barnum (1953), who have an extensive experience in the radiological analysis of cranio-vertebral anomalies, consider platybasia present when the basal angle equals or exceeds 145 degrees.

In the present study lines were drawn from the superior surface of the dorsum sellæ to the nasion and to the anterior lip of the foramen magnum. (Occasionally the latter point could only be identified on the mid-sagittal tomogram, being obscured by the petrous bones in the plain lateral radiograph). The basal angles varied between 112 degrees and 140 degrees. *No case of platybasia was encountered.*

In Table I are recorded the basal angles of those patients considered to have basilar impression. (The criteria used in making this diagnosis will be discussed later.) No correlation could be established between the basal angle and such presumed indices of basilar impression as the relation of the tip of the odontoid to Chamberlain's line, McGregor's line or the "digastric" line. Nor was there any correlation between the

TABLE I.—COMPOSITE ASSESSMENT OF BASILAR IMPRESSION AND COMPARISON OF VARIOUS RADIOGRAPHIC INDICES (VID. TEXT).

The cases are arranged in order of increasing "McGregor measurements."

Occ.=Occipitalization. D.I.=data incomplete. NM=not measurable

| *McGregor measurement (in mm.)* | *Bull's angle (in degrees)* | *Boogard's angle (in degrees)* | *Basal angle (in degrees)* | *Digastric measurement (in mm.)* | *"Tracing" from antero-posterior tomogram* | *Case* |
|---|---|---|---|---|---|---|
| 0 | −7 | 118 | 120 | −1 | ++ | 7 |
| 5 | 5 | 130 | 138 | −4 | + | 8 |
| 5 | 10 | 130 | 124 | −2 | + | 2 |
| 5 | 15 | 125 | 116 | −17 | D.I. | 21 |
| 6 | 37 | 140 | 132 | 2 | D.I. | 3 |
| 8 | 19 | 150 | 140 | 5 | + | 9 |
| 8 | 5 | 141 | 124 | −8 | + | 22 |
| 10 | 32 | 150 | 138 | −5 | D.I. | 18 |
| 10 | Occ. | NM | 124 | NM | ++ | 17 |
| 10 | 21 | 125 | 113 | −6 | D.I. | 1 |
| 10 | 26 | 160 | 120 | 0 | D.I. | 4 |
| 10 | 13 | 155 | 130 | 14 | D.I. | 16 |
| 12 | 13 | 150 | 129 | −2 | ++ | 10 |
| 13 | Occ. | 152 | 122 | D.I. | D.I. | 23 |
| 14 | 35 | 154 | 135 | 2 | + | 14 |
| 14 | Occ. | 165 | 135 | 10 | + | 11 |
| 14 | 22 | 157 | 130 | 0 | D.I. | 5 |
| 15 | 28 | 155 | 125 | 10 | + | 6 |
| 20 | 23 | 160 | 118 | 7 | D.I. | 15 |
| +++ | NM | NM | NM | 10 | +++ | 13 |

basal angle and Bull's angle, Boogard's angle and the diagnostic "tracings" obtained from the antero-posterior tomograms.

The vast majority of patients with basilar impression, occipitalization of the atlas, atlanto-axial dislocation and malformations of the foramen magnum and upper cervical spine have a normal basal angle. This angle is therefore of little use in the diagnosis of cranio-vertebral anomalies. The clinical significance (if any) of platybasia remains obscure.

*The Measurement of Basilar Impression.*—In normal persons the basilar, condylar and squamous parts of the occipital bone incline downwards throughout the whole of their extent. Their free borders, constituting the rim of the foramen magnum, therefore lie "at the lowermost part of the posterior fossa" (Grant, 1940). The mid-sagittal point of the anterior rim—or basion—lies at a slightly higher level than the corresponding point on the posterior rim—or opisthion (Cunningham, 1931). A line joining these two points defines the antero-posterior plane of the foramen

magnum. When the head is held in the neutral position this plane slopes very slightly downwards, from basion to opisthion. (Quain, 1882; Topinard, 1895).

20 *patients in this series were considered to have basilar impression.* The assessment of whether a given patient has or does not have basilar impression is not always straightforward. Before discussing our findings in the forementioned cases, the classical methods used in the diagnosis of this anomaly will be described. It will be argued that these methods do not in fact directly measure an invagination of the rim of the foramen magnum *into* the cranial cavity, but that they usually denote an alteration in the plane of the foramen magnum. Although an anteriorly situated basilar impression is one of the commonest causes of an alteration in this plane, it is by no means the only one.

*Boogard's angle* (1865).—Boogard, beside measuring the basal angle, also described an angle defined by the intersection of the plane of the clivus with the plane of the foramen magnum. He found the normal range of variation of this angle to be 119·5 degrees – 136 degrees and considered higher values characteristic of basilar impression. Zuckerman (1955) has recently shown that this angle, which he calls the "foramino-basal" angle, varies with age, being smallest at birth, increasing during the first few years of life and then decreasing again. Boogard's angle is not much used nowadays. Its value, as an index of basilar impression, will be assessed further on.

*Chamberlain's line* (1939).—This is a line drawn, on the lateral radiograph of the skull, from the "dorsal lip of the foramen magnum to the dorsal margin of the hard palate." Chamberlain considered that projection of the odontoid process or body of the first cervical vertebra above this line constituted basilar impression.

Saunders (1943) in a review of 100 lateral radiographs of the skull found that the tip of the odontoid lay on occasion slightly above Chamberlain's line. The mean position was: —·94 mm. ±3·6 mm., the symbol minus denoting an odontoid below Chamberlain's line. Poppel *et al.* (1953) in a survey of 102 radiographs found the mean position of the tip of the odontoid to be at Chamberlain's line (·06 mm. ± 3·3 mm.) Bull (1955), basing himself on a study of 120 radiographs, gives the mean position as —2·86 mm. ± 3 mm.

Two minor drawbacks to the use of Chamberlain's line are (*a*) that the posterior lip of the foramen magnum, one of the points of reference, is often difficult to define in the average lateral radiograph, and (*b*) that in certain types of basilar impression the posterior lip of the foramen magnum is itself invaginated. It is obviously a disadvantage in assessing such an abnormality to have a point of reference that may itself be mobile.

*McGregor's line* (1948).—McGregor proposed substituting for. Chamberlain's line a line drawn "from the upper surface of the posterior edge of the hard palate to the most caudal point of the occipital curve in the true lateral X-ray." This line has the undoubted advantage over Chamberlain's line that the posterior point is both fixed and easy to define. For these reasons, McGregor's line rather than Chamberlain's line has been used in assessing the relative value of various proposed indices of basilar impression. The term "McGregor measurement" will be used to denote the height of the upper end of the odontoid above McGregor's line.

McGregor, basing himself on the radiographs of 203 Bantu skulls, found the mean position of the odontoid to be $-1{\cdot}32$ mm. $\pm 2{\cdot}62$ mm,. in relation to his base line, the symbol minus again denoting an odontoid below the base-line. Bull (1955) found the mean position of the tip of the odontoid, in relation to McGregor's line to be $-{\cdot}39$ mm. $\pm 3{\cdot}02$ mm.

*Bull's angle* (Bull, 1946, 1951, Bull *et al.*, 1955). Bull has described an angle determined by the plane of the hard palate and the plane of the atlas vertebra. Bull, Nixon and Pratt (1955) measured this angle on the lateral radiographs of 120 normal skulls and concluded that patients with angles of 13 degrees or more (the mean plus three times the standard deviation) should be considered as having basilar impression.

Bull (1951) had earlier advocated the use of an angle determined by Chamberlain's line and the plane of the atlas. He stated that in normal persons these lines "are found to be parallel or nearly so . . . Chamberlain's line lying above." "In occipital condylar invagination the lines cross owing to the upward tilt of the anterior border of the atlas as it follows the invaginated condyles." In the present study the angle between the plane of the palate and the plane of the atlas was measured wherever possible, and this is the angle referred to as Bull's angle.

Several major criticisms can be levelled at attempts to define basilar impression from lateral radiographs of the skull. Both Chamberlain's line and McGregor's line are drawn from the posterior edge of the hard palate. This point is easy to define and conveniently situated *but it is not part of the base of the skull.* Now basilar impression, by definition, is an abnormality in which parts of the base (the rim of the foramen magnum and occasionally the adjacent area) are displaced in relation to the remainder of the base. The posterior edge of the hard palate is not a suitable landmark to use when defining these altered relationships. Its position is variable and its relation to the base inconstant, depending on the development of the facial bones. It can readily be shown that the distance between the dorsum sellæ and the hard palate may vary considerably. One of us (A. M. J.) measured this distance in 30 lateral radiographs of normal adult skulls taken at random from the files, and found it to range from

XUM

4·8 cm. to 6·5 cm. Although the odontoid is situated far back along the line joining the posterior edge of the hard palate to the lowermost part of the squamous occiput, there is little doubt that a low palate may give rise to a false diagnosis of basilar impression, if McGregor's line alone is used. Conversely, in the presence of a high palate, certain cases of basilar impression may be missed.

The importance attributed to a "high odontoid" in the diagnosis of basilar impression from the lateral radiograph also calls for some comment. The odontoid represents the body of the atlas and variations in the position of the odontoid usually reflect variations in the position of the anterior rim of the foramen magnum. A "high odontoid" may be seen however without elevation of this anterior rim, namely:

(*a*) *in patients with an abnormally long odontoid.* We have seen one such patient in whom the odontoid extended a full 5 mm. above the uppermost point of the anterior arch of the atlas. Such an abnormally long odontoid may be present without other anomaly of the cranio-vertebral junction.

(*b*) *in patients with occipitalization of the atlas.* When the anterior arch of the atlas is fused to the anterior rim of the foramen magnum, the odontoid lies higher than usual. In our experience this may in itself lead to a positive McGregor measurement, whether or not there is an associated elevation of the rim of the foramen magnum.

Even when a "high odontoid" truly reflects a high position of the anterior rim, it is doubtful whether basilar impression is invariably present. The basion (the mid-sagittal point of the anterior rim) may lie higher than usual without elevation, *into* the cranial cavity, of the bony structures bordering the foramen—in other words without basilar impression. In patients with a short clivus, for instance, the basion will be situated at a higher level than in patients with a long clivus. These patients will have a foramen magnum of steeper slope. They are, because of this, particularly liable to be misdiagnosed as cases of basilar impression. Two such patients were encountered, in the course of this study, and on each occasion basilar impression was seriously considered until antero-posterior tomography had shown that there was in fact no invagination of the rim. A positive Boogard's angle and a high reading of Bull's angle were merely indices of an increase in the slope between basion and opisthion.

As stated previously, no case of true platybasia was seen but it is quite possible that a *marked* increase in the basal angle of the skull would cause some elevation of the basion and an increase in the slope of the foramen magnum. Whether this state of affairs would constitute a true invagination of the anterior rim is a matter for speculation.

Boogard's angle and Bull's angle may likewise lead to erroneous diagnoses of basilar impression.

XUM

(*a*) *Boogard's angle* (often difficult to assess without a lateral tomogram) is increased in patients showing an abnormal slope of the foramen magnum. In such patients there may be no genuine invagination of the rim. (On the other hand, occipitalization of the atlas and abnormally long odontoids will not give rise to false diagnoses of basilar impression when Boogard's angle is used. In this sense an increase in Boogard's angle is perhaps a more reliable index of basilar impression than a positive "McGregor measurement."

(*b*) *Bull's angle*. It is generally assumed that the position of the head has little effect on the relative position of the two lines subtending this angle. No systematic attempt was made, in this study, to investigate the assumption. Variations in Bull's angle with the position of the head were encountered on several occasions however.

Bull measured his angle on routine "lateral skull" films, i.e. on films taken with the patient prone, the head in the "true lateral position." In the present series the films used were "laterals of the cervical spine," centred on C2 and taken with the patient erect. Many of our cases had a dorsal kyphosis. Compensatory lordosis of the cervical spine often resulted in an abnormal tilt of the plane of the atlas. These patients also tended to flex the head at the atlanto-occipital articulation in order to maintain a horizontal gaze. This combination of cervical lordosis and flexion of the head at the atlanto-occipital articulation may give rise to an abnormally high value for Bull's angle, whether basilar impression be present or not. We have observed Bull's angle to vary with the position of the head on two occasions. In the first case (congenital cervical synostosis with post-traumatic tetraplegia; not included in the present series) the angle varied from 12 degrees to 28 degrees. In the second case (Case 20) from 1 degree to 22 degrees. In each case the smaller value was recorded on a "lateral skull" film and the higher on a "lateral of the cervical spine."

Discussion has so far been confined to the diagnosis of basilar impression from the lateral radiograph of the skull. In 1941 Lindgren pointed out that impression could be confined to the parasagittal "weight-bearing" part of the rim of the foramen magnum and that it was certainly present when "a displacement of the region around the foramen magnum has reached such a degree as to be discernible on a frontal picture." In cases of primary basilar impression one does not know, of course, whether the condylar portion of the foraminal margin has "given way" as a result of weight-bearing during life. There is no direct evidence on this point. We suspect however, that the anomaly is not the result of a process of invagination but that, like a depression of the sternum, it is a congenital malformation.

Lindgren's observation, amply confirmed, has stimulated attempts to establish the diagnosis of basilar impression from antero-posterior

radiographs and tomograms. In addition to being of value in demonstrating elevation of the parasagittal condylar region, the antero-posterior films also have the advantage over lateral radiographs that they permit base lines to be drawn between points directly related to the floor of the posterior fossa. Two further radiographic indices of basilar impression have thus been suggested:

*Fischgold's line.*—Fischgold and Metzger (1952) pointed out that in the antero-posterior film of the skull (or better still in the transoral projection) a line joining the lower extremities of the mastoid processes passed through the atlanto-occipital articulations and that the tip of the odontoid was often situated on the same line. In cases of basilar impression, one or both atlanto-occipital articulations are elevated above this base-line. In view of the variability in the size of the mastoid processes, the authors later proposed a more constant base-line, drawn between the two digastric grooves (each groove is situated at the junction of the medial aspect of the mastoid process with the base of the skull). This *digastric line* can often be drawn on a good transoral film and is nearly always easy to define on an antero-posterior tomogram. We are not aware of any statistical analyses of the situation of the normal odontoid in relation to these two lines. An obvious reason why this has not been performed is that tomography of the skull base is a complicated and expensive procedure, not readily applicable to large numbers of controls. In the experience of those familiar with the technique, the digastric line usually passes well above the odontoid and occipital condyles.

*Antero-posterior tomograms of the base of the skull* are of the greatest value in the diagnosis of basilar impression. Only such films enable one to identify the actual rims of the foramen magnum. Serial tomographic cuts will outline the elevation of the rims and show the upward sweep of the floor of the posterior fossa towards the foramen magnum.

We feel that Chamberlain's line, McGregor's line, Fischgold's line and the "digastric line" are useful in assessing the position of the odontoid, a high-lying odontoid being common in basilar impression but occurring also from other causes. Increases in Boogard's angle denote either a true impression or an increase in the slope of the foramen magnum. Bull's angle may exceed 13 degrees in true basilar impression but also in patients with an abnormal slope of the foramen and in certain patients with a marked cervical lordosis. *Antero-posterior tomography of the foramen magnum is the only certain way of diagnosing basilar impression.* In the present series tracings on paper were made from the tomograms and when viewed serially it was found that they provided a good idea of the overall shape of the floor of the posterior fossa. A "positive tracing" means a direct demonstration of elevation of the rims of the foramen. It was observed in 11 patients. In 9 further patients, tomographic data were lacking or inadequate and the diagnosis of basilar impression was based

XUM

upon more orthodox findings (namely, if the odontoid lay 9 mm. or more above McGregor's line or if Bull's angle measured 13 degrees or over as suggested by Bull *et al.*, 1955). Possible causes of false positive readings such as short clivus, assimilation of the anterior arch of the atlas and abnormally long odontoid were taken into account, several cases being excluded on these grounds. Basilar impression was never diagnosed, whatever the "McGregor measurement" or Bull's angle, if antero-posterior tomograms showed a normal foraminal rim.

### Contrast Studies

Myelography, encephalography or vertebral angiography were performed in the majority of the cases here reported. They contributed information concerning the presence of neural malformations underlying the skeletal defects and the manner in which the latter might be affecting the neuraxis. These investigations were helpful in assessing the likelihood of surgery being beneficial.

*Myelography* was performed (by the lumbar route) on 15 patients. Two patients (Cases 11 and 12) showed an almost complete block at the level of the foramen magnum: both patients had occipitalization of the atlas and chronic atlanto-axial dislocation. In one patient (Case 22) the presence of a cervical syrinx was disclosed. In 4 patients (Cases 16, 18, 19 and 22) ectopia of the cerebellar tonsils was demonstrated by a posterior filling defect in the uppermost part of the cervical canal. With the patient screened in the supine position no contrast entered the cisterna magna at considerable angles of tilt. In 2 patients (Cases 8 and 9) a partial hold up of the contrast occurred at the apex of a dorsal kyphos or scoliotic angulation and it was thought that part at least of the neurological disability arose at this site, rather than at the level of the cranio-vertebral anomaly. The remaining patients had a normal myelogram.

*Encephalography* was performed in 12 patients. In one patient (Case 7) symmetrical enlargement of the ventricular system was present. In 8 patients (Cases 16, 17, 18, 19, 20, 22, 23 and 24) the ventricles failed to fill. Seven of these cases were considered, on various grounds, to have ectopia of the cerebellar tonsils. Operation was performed on 4 of them (Cases 17, 18, 19 and 22) and cerebellar ectopia was present in each case.

*Vertebral angiography* was attempted on 11 patients and was successful in 7 instances. In 4 patients no specific abnormality was demonstrated other than the rather tortuous course of the vertebral artery. In 3 patients (Cases 18, 19 and 20) the posterior inferior cerebellar artery was seen to enter the upper part of the spinal canal and to descend for a certain distance before regaining the cranial cavity. (This we have called the "loop sign"). Each of these three patients had

XUM

cerebellar ectopia. This "loop sign" may be seen in cases of foraminal pressure cone—or it may sometimes be a normal variant—but its presence in each of these 3 patients with proved cerebellar ectopia suggests that vertebral angiography may be of value in detecting this anomaly. Scoville and Sherman (1951) reported 10 cases of "platybasia" and found that "herniation" of the cerebellum into the cervical canal was present in each of the 8 patients subjected to high cervical laminectomy. They observed, moreover, "the presence in all cases of an anomalous redundant posterior inferior cerebellar artery which may completely traverse the dorsal surface of the tonsils." Bagley and Smith (1951) however, noted that in their patient (with basilar impression, a syringomyelic syndrome and unilateral cerebellar herniation to C3 level) this artery was not displaced. Gardner and Goodall (1950) do not mentioned the artery in their series of 17 cases of the Arnold-Chiari malformation which came to operation.

## Classification

For purposes of description and analysis we have attempted to divide the patients into a number of groups. This proved difficult because (1) several skeletal defects were often found to coexist in a given case, (2) under such circumstances it was not easy to decide which, if any, of the bony lesions was of neurological significance, and (3) in a number of cases a neural abnormality was found to underlie the skeletal defect. Nevertheless, after full investigation (often including tomography, encephalography, vertebral angiography and myelography) as precise a diagnosis as possible was made in each case. We attempted in particular to differentiate patients with purely skeletal anomalies from those thought to have, in addition, underlying neural defects such as malformations of the hind-brain. In several cases further information became available at operation or autopsy.

The cases were divided into 4 groups:

*Group I.* Isolated primary basilar impression with neurological signs. Cases 1–9.

*Group II.* Multiple anomalies with neurological signs. Cases 10–14.

*Group III.* Cerebellar ectopia with or without skeletal anomalies. Cases 15–22.

*Group IV.* The Klippel-Feil syndrome. Cases 23–24.

### Group I. *Isolated Basilar Impression with Neurological Signs*

This group consisted of 9 patients (Cases 1 to 9); basilar impression was the sole anomaly of the cranio-vertebral junction.

(*a*) Seven of the 9 patients showed physical signs of cervical syringomyelia or syringobulbia.

XUM

TABLE II.—ISOLATED BASILAR IMPRESSION WITH NEUROLOGICAL SIGNS (GROUP I)

| *Case* | *Sex* | *Age* | *Duration of symptoms (in years)* | *Clinical features* | *Comments* |
|---|---|---|---|---|---|
| 1 | M | 31 | 10 | Syringomyelia | – |
| 2 | M | 17 | 2 | Syringobulbia | – |
| 3 | M | 34 | 9 | Syringomyelia and syringobulbia<br>Chronic papillœdema | Gross atrophy of cord at operation |
| 4 | M | 35 | 12 | Syringomyelia and syringobulbia | Onset of symptoms following trauma |
| 5 | M | 33 | 2 | Syringomyelia | – |
| 6 | M | 41 | 8 | Syringomyelia | – |
| 7 | F | 31 | 4 | Syringomyelia<br>Hydrocephalus. Fits | Radiological evidence of raised intracranial pressure. |
| 8 | M | 34 | 2 | Gross kypho-scoliosis with cord signs | Myelographic block at apex of dorsal kyphos. |
| 9 | M | 29 | 12 | Gross kypho-scoliosis<br>Cerebellar syndrome<br>Syringomyelia | Myelographic block at apex of dorsal kyphos. |

(*b*) The clinical picture of syringomyelia was encountered with basilar impression of very varying degrees. The range of skeletal anomaly did not differ significantly from that observed in patients without neurological disorder. We may therefore conclude that the association between basilar impression and syringomyelia is not usually one of cause and effect.

(*c*) Two patients (Cases 8 and 9) showed extreme degrees of dorsal kyphoscoliosis. Manometric and myelographic observations suggested that the curvature of the spine itself may have contributed to the sign elicited in the lower limbs. The neurological syndromes were complex and probably due to myelodysplasia.

GROUP II. *Multiple Skeletal Anomalies at the Cranio-vertebral Junction and Neurological Signs*

In this group there were 5 patients (Cases 10–14). Four had various degrees of occipitalization of the atlas. Four (Cases 10, 11, 13 and 14) also had basilar impression. In three (Cases 10, 12 and 13) there were fusions of cervical vertebræ. Atlanto-axial dislocation was present in 2 of the patients (Cases 11 and 12). Two patients (Cases 10 and 13) had marked dorsal scoliosis.

Clinically, these cases were diverse; one patient (Case 13) had few signs and little disability, despite gross skeletal anomalies (fig. 15).

XUM

TABLE III.—MULTIPLE SKELETAL ANOMALIES WITH NEUROLOGICAL SIGNS (GROUP II)

| *Case* | *Sex* | *Age* | *Clinical features* | *Basilar impression* | *Occipitalization* | *Atl.-axial dislocation* | *Fusions* | *Spina bifida* | *Comments* |
|---|---|---|---|---|---|---|---|---|---|
| 10 | F | 37 | Syringomyelia and syringobulbia<br>Vertical nystagmus and oscillopsia | + | + | 0 | C2–C3<br>C7–D1 | 0<br>0 | — |
| 11 | M | 36 | Syringomyelia.<br>Gynæcomastia.<br>Vertical nystagmus and oscillopsia | + | + | ++ | 0 | 0 | Myelographic evidence cord compression at foramen magnum. Operation. Posterior dural band |
| 12 | M | 54 | Spastic tetraparesis.<br>Marked sternomastoid fasciculation | 0 | + | + | C2–C3 | 0 | Partial myelographic block at foramen magnum |
| 13 | M | 29 | No symptoms.<br>Slight pyramidal signs.<br>Congenital absence right thumb | + | + | 0 | C3–C5 | 0 | — |
| 14 | F | 62 | Syringomyelia<br>Soft tissue and bony hypertrophy of right arm | + | 0 | 0 | 0 | C1<br>C2 | Onset disability at age 53 |

Three patients (Cases 10, 11 and 14) presented as cases of syringomyelia. The fifth patient (Case 12) was remarkable in that he had a purely motor syndrome with marked spasticity of all four limbs.

Myelography was performed in four of the five patients and showed a block at the level of the foramen magnum in two instances.

GROUP III. *Cranio-vertebral Anomalies associated with Cerebellar Ectopia*

This group consisted of 8 patients (Cases 15 to 22). Cerebellar ectopia was found at operation in 5 patients; in 3 the evidence was mainly radiographic. In the cases that came to operation the lowermost pole of cerebellar tissue was at least 2 cm. below the foramen magnum in each instance. In Case 19 a myelographic block had occurred as low as C4.

XUM

TABLE IV.—CRANIO-VERTEBRAL ANOMALIES ASSOCIATED WITH CEREBELLAR ECTOPIA (GROUP III)

| *Case* | *Sex* | *Age* | *Clinical features* | *Skeletal anomaly* | *Operative findings* |
|---|---|---|---|---|---|
| 15 | M | 22 | Cord compression at foramen magnum | Basilar impression<br>Posterior spina bifida of atlas | Cerebello-medullary ectopia (2 cm.)<br>Intramedullary cyst<br>Arachnoidal adhesions |
| 16 | M | 26 | Slight pyramidal syndrome<br>Vertical nystagmus with oscillopsia | Basilar impression | – |
| 17 | M | 28 | Cervical radiculopathy<br>Mirror-movements<br>Vertical nystagmus<br>Congenital thenar hypoplasia | Basilar impression<br>Occipitalised atlas<br>Odontoid fused to clivus | Cerebellar ectopia (2 cm.) |
| 18 | F | 48 | Vertical nystagmus with oscillopsia | Basilar impression | Cerebello-medullary ectopia (2·5 cm.)<br>Arachnoidal adhesions |
| 19 | M | 31 | Slight bulbar and pyramidal syndrome<br>Vertical nystagmus with oscillopsia | Dolichocephaly<br>"Flat" posterior fossa | Cerebello-medullary ectopia (5 cm.)<br>Dural band |
| 20 | M | 7 | Slight cerebellar syndrome<br>Mirror-movements | Large foramen magnum<br>Spina bifida C4 | – |
| 21 | F | 34 | Syringomyelia<br>Vertical nystagmus<br>Late intracranial hypertension | Basilar impression | Cerebello-medullary ectopia (2 cm.)<br>Membrane occluding foramen Magendie<br>Extensive syringomyelia |
| 22 | M | 26 | Syringomyelia | Basilar impression<br>Anterior spina bifida of atlas | Cervical syrinx<br>Arachnoidal adhesions |

The tonsils were described as "tongue-like," "thin," "flat," "atrophic," and their appearance "quite unlike that of herniated tonsils." In several of the cases there is mention of meningeal thickening, dural bands or arachnoidal adhesions at the level of the foramen magnum, often causing obvious constriction of the ectopic cerebellar tissue. In 3 of the 5 patients submitted to operation, part of the medulla was lying in the spinal canal and the uppermost cervical roots followed an abnormal upward course.

Basilar impression was the commonest cranio-vertebral anomaly in these 8 cases, being present in 6. One patient (Case 17) also had occipitalization of the atlas with fusion of the odontoid to the clivus. In another patient (Case 20) the skeletal anomalies consisted of a concave clivus, large foramen magnum, capacious upper cervical canal and cervical spina bifida (fig. 18).



XUM

The degree of tonsillar ectopia did not appear to be related, in any obvious way, to the type or severity of the associated skeletal defect. For example, Case 17 had marked skeletal anomalies in the region of the foramen magnum but only 2 cm. of cerebellar ectopia, whereas Case 18, with cerebellar tonsils extending down to C4 showed only minimal bony abnormalities.

The clinical aspects of these 8 cases were rather variable. Vertical nystagmus occurred in over half of them and will be discussed later. Papillœdema was found in only 1 patient (Case 21). No patient had complained of suboccipital pain. We think this is because the neural defect was often discovered incidentally, in the course of radiographic investigation of patients with cranio-vertebral anomalies or during operation on such patients. In a number of other published cases symptoms and signs of intracranial hypertension had already developed before investigations were completed.

Two of these 8 patients (Cases 21 and 22) had symptoms and signs of syringomyelia (in the former case a syrinx was found at autopsy). In a third patient (Case 15) a large syrinx was found at operation from which fluid was readily aspirated although the patient had shown no signs of clinical syringomyelia. Two patients showed ataxia of the limbs and pyramidal signs were present in 4.

TABLE V.—CEREBELLAR ECTOPIA IN PATIENTS WITH CRANIO-VERTEBRAL ANOMALIES. The symbol – denotes that the particular investigation was not performed

| *Case* | *Myelogram* | *Encephalogram* | *Vertebral angiography* | *Operative confirmation* |
|---|---|---|---|---|
| 15 | – | Normal | Unsuccessful | Yes |
| 16 | *Block C1* | No ventricular filling (twice) | – | Radiographic diagnosis |
| 17 | – | No ventricular filling (twice) | – | Yes |
| 18 | *Block C1* | No ventricular filling (once) Wide sulci | "Loop" sign | Yes |
| 19 | *Block C4* | No ventricular filling (once) | "Loop" sign | Yes |
| 20 | Cervical meningocele | No ventricular filling (once) | "Loop" sign | Radiographic diagnosis |
| 21 | – | Ventriculography: dilated 3rd and 4th ventricles | – | Yes |
| 22 | *Block C1* | No ventricular filling (once) | – | Radiographic diagnosis |

The diagnosis of tonsillar ectopia was often first suggested by certain radiological findings. These comprised (*a*) repeated failure to fill the ventricles during air encephalography, (*b*) a partial posterior obstruction in the upper cervical canal at myelography and (*c*) an aberrant course of the posterior inferior cerebellar artery, demonstrated by vertebral angiography—the findings occurring in various combinations. In those cases submitted to operation, diagnoses based on such radiological criteria were fully substantiated (Table V).

GROUP IV. *The Klippel-Feil Syndrome*

There were 2 patients (Cases 23 and 24) in this group. Each had the characteristic features of short neck, low hair-line and extensive fusion of cervical vertebræ. Case 23 (figs. 8 and 9) had developed slight spastic weakness of the lower limbs while in his early twenties. There was a suboccipital scar where "a cyst" had been removed in infancy, nystagmus was present and air failed to enter the ventricular system on lumbar encephalography. It is possible therefore that he had cerebellar ectopia. The basal angle was 120 degrees, there was basilar impression and the posterior arch of the atlas was occipitalized.

Case 24 was a boy of 9 (figs. 10 and 11) with a large foramen magnum, short neck, low hair-line and extensive cervical fusions with spina bifida. Two siblings had had meningoceles and the mother had also given birth to an anencephalic fœtus which had not survived. The patient had suffered from fits in infancy. He had a bilateral abducens palsy, probably resulting from nuclear agenesis, a high palate with a nasal voice and was periodically incontinent of fæces. There was no nystagmus. He showed mirror-movements of the hands. The ventricles failed to fill at encephalography, performed by the lumbar route.

## CLINICAL OBSERVATIONS

(1) *The Physical Appearance*

Although many patients with skeletal defects in the region of the foramen magnum have a perfectly normal appearance, others show features which should suggest the presence of an anomaly, for instance an unusual posture of the head, an abnormal configuration or restricted mobility of the neck, or an altered position of the hair-line (Plate III, figs. 1, 2, 3, 4, and 5). There may be stigmata in other parts of the body. In this series the neck was abnormally short in five cases (6, 13, 17, 23 and 24); there was a lateral tilt of the head in six (10, 11, 12, 13, 17 and 18); the hairline was low in six (6, 11, 15, 16, 23 and 24). Occasionally the shortness of the neck deceived us (as in the case of a young obese girl with lumbo-sacral syringomyelia)—into anticipating a cranio-vertebral anomaly which did not exist. Webbing of the neck in a case of Turner's syndrome prompted a colleague to refer a patient to one of us as an example of a

XUM

cranio-vertebral anomaly: none was present. A cervical lordosis compensating a dorsal kyphosis occasionally made the neck appear short (a cranio-vertebral anomaly was sometimes in fact also present). In the 2 cases in which the neck was grossly short the characteristic radiological features of the Klippel-Feil Syndrome were present. Otherwise an abnormally short neck could not be correlated with any specific type of cranio-vertebral anomaly. No patient, however, with occipitalization of the atlas had a normal-looking neck.

Occipitalization of the atlas was present in 5 of the 6 cases with noticeable tilting of the head. Bertolotti (1920) and Feil (1921) were among the first to comment on "bony torticollis" and considered that the tilt resulted from the asymmetrical synostosis of the lateral masses of the atlas to the base of the skull. In our cases, asymmetrical basilar invagination was occasionally associated with tilting of the head. In one of our patients unequal development of the axis vertebra seemed to be responsible. No instances of cervical hemivertebra or of "paramastoid process" of the occipital bone were encountered—defects sometimes found in association with cranio-vertebral anomalies and said to produce a head tilt. Elevation of one shoulder was noted in 3 of our cases (3, 13 and 17); in Case 3 it was an example of "Sprengel's deformity" and in Cases 13 and 17 it resulted from scoliosis.

A number of patients in this series showed a *low hair-line* but, with the possible exception of Case 15, all such patients had clinically normal neck. We have not found a low hair-line to be a sign of much assistance. In the majority of cases a low hair-line is a clinical corrollary of a short neck and does not actually represent an extension of the hair-producing properties of the scalp to the posterior parts of the upper cervical dermatomes.

A small tuft of hair in the mid-line, some way down the back of the neck, should raise the possibility of an underlying spina bifida (fig. 7).

*Webbing* of the neck has occasionally been recorded in patients with cranio-vertebral anomalies. The term had been used in the literature to denote either a thin sheet of skin or fibrous tissue stretched out between the region of the mastoid and the shoulder—or alternatively to describe the triangular appearance of the neck resulting from abnormal splaying of the upper fibres of the trapezius muscles. Webbing of the first type was not encountered in this series but abnormal splaying of the trapezii was not uncommon. Atrophy of the sternomastoid muscles, by exaggerating the hollow appearance of the supraclavicular fossæ may throw the trapezii into prominence.

Stigmata such as facial asymmetry, malformation of the ears, abnormal palates, congenital absence of thenar muscles or of digits were met with in several of our patients.

XUM

(2) *Postural Loss in the Upper Limbs*

"Syringomyelic" patterns of sensory disorder in patients with craniovertebral anomalies were observed by Schuller (1911) in his second case and have since been recorded by many writers (Meier, 1929; Bau-Prussak and Fizhaut-Zeldowickz, 1938; Chamberlain, 1939; Dereymaeker, 1940; Gustafson and Oldberg, 1940; Peyton and Peterson, 1942; Ray, 1942; Meyer, 1944; Mayerszky, 1949; Gvozdanovic and Dogan, 1951; Garcin and Oeconomos, 1953; McRae, 1953; Phillips, 1955). It was present in 12 of our patients (Cases 1, 3, 4, 5, 6, 7, 9, 10, 11, 14, 21 and 22).

We wish to draw attention to a different type of sensory disturbance observed in 6 of our patients (Cases 3, 9, 10, 11, 14 and 15) and which has also been recorded in a number of previous reports. Of these 6 patients, the most severely affected (Case 15) had no superficial sensory loss. A second patient (Case 11) had slight tactile and spinothalamic loss in one hand in addition to gross postural loss. The other 4 patients had hypalgesia and thermanalgesia affecting one or both hands.

These 6 patients had loss of postural sense in the fingers and wrists causing marked "sensory clumsiness." The postural loss was associated in all instances with gross impairment of vibration sense in the hands and sometimes with lesser degrees of pallanæsthesia in the lower limbs. In all 6 patients the degree of proprioceptive defect in the hands and fingers was far in excess of any present in the legs. Thirteen further patients showed impairment of posterior column sensation confined to the lower extremities, or present more diffusely, but these are excluded from the present considerations.

Five of the 6 patients in question suffered from a veritable stereoanæsthesia, unilateral in 2 cases (9 and 11) and bilateral in the other 3 (3, 10 and 15). In 1 patient (Case 15) the sensory disturbance was the presenting symptom. This patient had difficulty in feeding himself and dressing. He could not help himself to soft-centred sweets without squashing them, could not deal cards, and would often drag the lining out of his pocket when searching for coins. Another patient in this group (Case 11) would cycle to work regularly but had to look periodically at his right hand to ensure it had not wandered from the handlebar brake! He typifies the forementioned disparity between the degree of postural loss in the upper limbs and that in the lower.

In 2 of these 6 patients basilar impression was the sole skeletal anomaly (Cases 3 and 9). In Case 15 operation revealed an ectopia of the cerebellar tonsils and obstruction at the level of the foramen magnum. In Cases 10 and 11 there was, in addition to basilar impression, occipitalization of the atlas. In Case 11, a chronic atlanto-axial dislocation markedly narrowing the effective antero-posterior diameter of the foramen magnum. In Case 14 there was marked asymmetry of the foramen.

The basis of the symptom must be sought in the anatomical disposition

of abnormal susceptibility to compression, in the upper cervical cord, of those fibres conveying proprioceptive sensation from the upper limbs. Although this is not a common pattern of sensory loss it has been observed in compressive lesions at the level of the foramen magnum and was a conspicuous feature in 5 of the 7 patients reported by Symonds *et al.* (1937). These authors thought that defective posterior column sensibility practically confined to the upper limbs "may be a characteristic feature of compression of the cord at this (foramen magnum) level at certain stages of its development."

In the literature relating to cranio-vertebral anomalies this particular sensory syndrome has been observed by List (Case 4), Meyer (1 case), Mayerszky (Case 2), Girard *et al.* (1949; 1 case), O'Connell and Turner (Case 4). (The last-named authors, incidentally, did not find any instance of dissociated sensory loss of syringomyelic type in their 5 cases.) In 3 of the patients described by Garcin and Oeconomos there was profound disturbance of postural sensation in the upper limbs. Lastly, McRae in describing 17 cases of occipitalization of the atlas with neurological signs mentions that 4 patients had "posterior column signs" confined to the arms and that 6 patients had "reduction of two-point discrimination or stereognosis in the hands". McRae and Barnum on the other hand found posterior column signs infrequently and suggested "that the main damage to the cord was occurring anteriorly, presumably by the displaced odontoid process of the axis, rather than posteriorly by the dural band. Not all the cases showing posterior column signs had a dural band or cerebellar tonsillar herniation posteriorly."

*Mirror Movements of the Hands:*

Dr. R. J. Isaac drew our attention of the occasional occurrence of mirror movements of the hands in cases of the Klippel-Feil syndrome when he referred a patient (Case 20), exhibiting this disturbance, who proved to have an Arnold-Chiari type of malformation. One of us (C. P.) subsequently observed it in another patient (Case 17) in whom its existence had not been previously detected. A third patient showing mirror movements with a characteristic Klippel-Feil syndrome has now been seen.

The 3 patients showed no paresis or spasticity in upper or lower limbs; there were no signs of "pyramidal" disorder or of mental deterioration. The mirror movements were of lesser amplitude than those initiated by volition, but were otherwise similar in every respect. They could be elicited as easily from one hand as from the other and never showed any tendency to "overflow" into other muscle groups of the ipsilateral or contralateral limb. They were co-ordinate to a high degree and in this resembled physiological movements. They did not have the unnatural appearance of the crossed synkineses of pyramidal disease and little effort

XUM

was required for their production. Extension of the index finger of one hand would for instance be accompanied by immediate extension of the index, and the index only, of the other hand. Movements could be "mirrored" whatever the frequency of the initiating contraction. "Piano-playing," movements of abduction or adduction of the fingers, or flexion and extension of the wrists, or of pronation and supination of the forearms were all simultaneously performed on the opposite side. One of the patients could not climb a ladder, this task requiring a high degree of dissociation between the activity of one hand and that of the other. The same difficulty in climbing a ladder was observed by one of Smith's (1947) patients and by one of Willard and Nicholson's (1934) patients. Both these patients were troubled by "mirror movements" of the hands but only the second was an example of the Klippel-Feil syndrome. The first was normal apart from "mirror movements."

Bauman (1932) appears to have been the first to describe "inability to dissociate the movements of the two hands" in the Klippel-Feil syndrome. This was present in 4 of the 6 children he described with gross fusions of the cervical vertebræ: cervical spina bifida was present in 3 of them. Bauman thought that the symptom of mirror movements was so frequent in his cases and so rare in other conditions that it was reasonable to conclude that it had been overlooked in many reported cases of Klippel-Feil syndrome. He considered it should be included in the symptom-complex of this condition. Willard and Nicholson (1934) and Erskine (1946) have each described a case of the Klippel-Feil syndrome showing "mirror movements" of the hands.

Only 1 of our 3 cases could be described as an example of the Klippel-Feil syndrome (Case 24). Case 17 had basilar impression and occipitalization of the atlas; the dens was fused to the clivus and the spinous processes of the upper cervical vertebræ were abnormal. Case 20 was an example of the Arnold-Chiari type of malformation—with a large foramen magnum, a capacious upper cervical spinal canal, a spina bifida at C4 and a cervical meningocele. The neck of each of these 3 patients was short.

Certain embryological considerations may throw some light on the nature of these movements. Erskine (1946) deals in great detail with the development of the cervical spine and underlying spinal cord, and emphasizes the extent to which the latter is dependent upon the former. He quotes Toro (1938) who showed that in many vertebrates the induction and formation of the central nervous system are under the influence of certain incompletely understood changes in the underlying mesoderm. This relationship only seems to pertain during an early phase of embryological development. These facts acquire special significance when one considers the fundamental bony defect in patients with the Klippel-Feil syndrome. Cervical spina bifida is a frequent finding in the Klippel-Feil

XUM

syndrome, and Feller and Sternberg (1932) state that the cervical spine frequently shows undoubted features of duplication. Erskine (1946) believes that the Klippel-Feil deformity may actually "represent a primary duplication of the axis with subsequent incomplete reunion." Recorded pathological examinations of the spinal cord in such patients are extremely rare. Avery and Rentfro (1936) observed a striking malformation of the cervical cord which consisted of two masses almost completely divided by a deep anterior fissure. The fibre pathways were not studied. It is not possible to say therefore how often the anomalies in the mesodermal structures (duplication and incomplete fusion) are associated with similar anomalies of the spinal cord. However, unusual neural dispositions are not unlikely and Erskine has suggested that "mirror movements" might result from "disorder of internal configuration" or "incomplete bilateral segregation of the cells of origin of the brachial plexus."

"Mirror movements" should not be regarded as an essential feature of the Klippel-Feil syndrome but rather as a sign of underlying neural defect when seen in patients with congenital anomalies of the cervical spine and cranio-vertebral junction.

*Vertical Nystagmus and Oscillopsia*

Fifteen of our 24 cases showed nystagmus on lateral gaze. In nine patients (Cases 4, 9, 10, 11, 16, 17, 18, 19 and 21) the nystagmus was of unusual type. In each instance there was nystagmus on lateral gaze, usually of an oblique or rotatory type, but in addition there was sustained vertical nystagmus, usually of large amplitude, often slow, and sometimes associated with oscillopsia. In 6 of these patients (Cases 10, 11, 16, 18, 19 and 21) the nystagmus was "spontaneous" (i.e. of second degree) and coarse enough in two to be seen from the foot of the bed. In 9 instances the movements occurred on looking down, in 4 on looking up.

Four of the 9 affected persons (Cases 10, 11, 18, and 19) were aware of the nystagmus and over a number of years had noticed oscillation of objects looked at. Three others were aware of occasional "jumpings" or "vibrating" in certain directions of gaze. In 2 instances (Cases 18 and 19) oscillopsia was the main symptom for which the patient sought relief. Both patients had developed a marked dislike for descending stairs; looking down would induce such an apparent oscillation of the steps as seriously to affect their self-confidence. One patient lessened the oscillopsia occurring on downward gaze by flexing his neck when walking. Following operation his vertical nystagmus almost entirely disappeared and his relatives commented on his more upright carriage.

Momentary diplopia was experienced by 4 of these patients but in none was there clinically demonstrable ophthalmoplegia. In 3 cases the position of the head appeared to have some effect on the vertical nystagmus, the sign being more marked in the upright than the reclining position.

XUM

Cerebellar dysarthria and intention tremor of the limbs were present in only 2 of the 9 patients with vertical nystagmus (Cases 4 and 9).

Herniation of the cerebellar tonsils was confirmed at operation and/or autopsy in 4 of these patients (Cases 17, 18, 19 and 21); in a fifth case (16) the encephalographic and myelographic evidence was considered definite enough to justify the diagnosis. Of the 6 patients with "spontaneous" nystagmus and oscillopsia, 3 had proved herniation of the cerebellar tonsils (Cases 18, 19 and 21) and 1 (Case 16) probable herniation.

Although vertical nystagmus has often been recorded in the protocols of patients with congenital abnormalities in the region of the foramen magnum few writers have commented on it. In each of the following references coarse vertical nystagmus was observed and there was either operative or post-mortem proof of cerebellar herniation (List, 1941: Cases 2, 5, 6 and 7; Craig *et al.*, 1942: 1 case, Custis and Verbruggen, 1944: 1 case; Girard *et al.*, 1949: 1 case; O'Connell and Turner, 1950: Case 5; Garcin and Oeconomos, 1953: Cases 7 and 17). Oscillopsia was probably present in the case described by O'Connell and Turner. Scoville and Sherman (1951) found in the majority of their 10 cases of "platybasia" "atypical coarse type of nystagmus frequently occurring with the eyes in the neutral position and changing its character or direction depending on whether the eyes are turned laterally, upwards or kept at rest." In 8 of their patients cerebellar displacement of "Arnold-Chiari type" was found at operation. The only other authors who have commented on the significance of vertical nystagmus are Burrows and Cogan (1954). They described 9 cases of "platybasia and the 'Arnold-Chiari malformation' " and observed that vertical nystagmus occurred in every case and that it varied with the posture of the head.

Vertical nystagmus is usually considered a sign of a mid-line brain-stem or cerebellar lesion. Disseminated sclerosis, syringomyelia or tumours of the posterior vermis probably account for most cases. As far as is known it does not arise in man from lesions of the labyrinths, although Spiegel and Scala (1944) reported its production in the cat following bilateral puncture of the oval windows or bilateral paralysis of the labyrinths induced by cocaine. Walsh *et al.* (1942) described coarse nystagmus in patients with basilar impression and cerebellar herniation. The patients, although ataxic, showed fair co-ordination on formal testing. The authors considered this particular association of physical signs suggestive of a "flocculo-nodular" disturbance. The majority of our patients with vertical nystagmus showed neither hypotonia nor intention tremor and 5 of the 9 cases with this type of nystagmus had cerebellar herniation.

## The Effect of Trauma

Many writers have recorded the development or aggravation of symptoms after trauma in patients with cranio-vertebral anomalies. In the

XUM

present series the actual onset of symptoms in Case 4 took place immediately after a fall of 20 feet during a Commando course. In Case 6 the patient had himself noticed an increase of disability for short periods after heavy falls. In three other cases with congenital fusion of some of the cervical vertebræ but without any cranio-vertebral anomaly (not included in the present series) severe episodes of tetraplegia occurred following minor trauma. One patient had in fact experienced two such attacks at an interval of nearly thirty years. Both made moderately good recoveries.

Critchley's (1926) patient, probably an example of the Klippel-Feil syndrome, developed an acute paraplegia after being involved in a brawl. List's (1941) fourth case, a man of 21 with occipitalization of the atlas and marked atlanto-axial dislocation, had twice suffered a transient tetraplegia after injury. In 2 of the 5 cases of basilar impression reported by O'Connell and Turner (1950) injury to the head appeared to have precipitated symptoms (Cases 2 and 3). Shoul and Ritvo (1952) also noted the effect of injury in 2 of their patients (Cases 7 and 8). The first had noticed that exercise often precipitated sudden weakness of his arms. Transient tetraplegia eventually followed a fall; he had fusion of the second and third cervical vertebræ and a hypoplastic odontoid. Their second patient, with a Klippel-Feil deformity, died suddenly after a fall and autopsy revealed fusion of the third, fourth and fifth cervical vertebræ; the odontoid and rim of the foramen magnum were fractured and the spinal cord lacerated. McRae (1953) reported that 2 of his patients with separate odontoids were liable to transient bouts of tetraplegia after trauma; he was not able to say, however, whether the abnormality itself was congenital or acquired. McRae and Barnum (1953) stated that 6 of their 25 cases with occipitalization of the atlas first developed symptoms after head or neck trauma. Phillips (1955) states that one of his 21 cases of basilar impression had a temporary tetraplegia following a fall eleven years before his admission to hospital (Case 15). Bachs *et al.* (1955) have recently commented on the delayed onset of myelopathy in case of chronic atlanto-axial dislocation whether the latter was congenital or due to trauma.

## The Relationship of Syringomyelia to Anomalies of the Cranio-vertebral Junction

It has long been known that anomalies of the spinal cord and vertebral column may occur in various combinations. In the so-called dysraphic disorders there is defective fusion of tissues in the dorsal medial region of the developing embryo. Cutaneous, mesodermal and neural malformations in the *longitudinal* plane occur. It is possible that true syringomyelia arises from a process of neural dysraphia. In syringomyelia there may also be defects at the cranio-vertebral junction. These frequently

take the form of some disturbance in the *transverse* plane such as anomalous segmentation. McRae (1953) found that 38 per cent of cases of syringomyelia and syringobulbia at the Montreal Neurological Institute had bony abnormalities in the region of the foramen magnum. Bull *et al.* (1955) found that 30 per cent of 37 cases of syringomyelia at the National Hospital, Queen Square, London, had basilar impression. We found 5 instances of such anomalies when we reviewed 28 cases of syringomyelia (18 per cent). Garcin and Oeconomos reviewed 112 case reports (published between 1901 and 1951) of various cranio-vertebral anomalies associated with neurological signs and found that a syringomyelic syndrome was present in 14·3 per cent of the cases. When occipitalization of the atlas was present the incidence of syringomyelia approached 25 per cent. Of our 24 patients, 12 showed a syringomyelic syndrome.

The nature of this association between a syringomyelic syndrome and anomalies of the cranio-vertebral junction is neither simple nor uniform. A syrinx is not always present and on the other hand intramedullary cavitation in the cervical region is not always a manifestation of "true" syringomyelia. The association may be considered under four headings.

(1) *Skeletal and Neural Defects are Not Directly Related*

The majority of cases are probably of this type; both defects are manifestations of disordered development. Mechanical interference with the neuraxis resulting from skeletal abnormality will not explain those cases (*a*) where basilar impression is of mild degree and the size of the foramen magnum is not reduced (Cases 5, 6) or (*b*) those cases where the syrinx is in the dorsal or lumbar segments of the cord or where there is extensive myelodysplasia (Case 8).

Myelography in these cases will show no evidence of obstruction at the level of the foramen magnum but may occasionally disclose cerebellar ectopia (Case 22).

(2) *Compression of the Neuraxis at the Level of the Foramen Magnum*

When this arises basilar impression is rarely the sole anomaly. There is usually occipitalization of the atlas or marked atlanto-axial dislocation which narrows the effective antero-posterior diameter of the foramen magnum. Myelography demonstrates the obstruction (Cases 11 and 12). Cerebellar ectopia may also be present but there is no syrinx.

(3) *Acquired Intramedullary Cavitation*

Intramedullary cavitation could also result from (1) ischæmic myelomalacia or (2) obstructive hydromyelia. Lichtenstein (1942) pointed out that in the former case the cavity is not lined by ependyma and gliosis is less pronounced than in "true syringomyelia." In this respect, Mr. Charles Langmaid has shown us a case in which osteogenesis imperfecta caused

XUM

gross basilar impression which resulted in tetraparesis and at operation intramedullary cavitation was a striking finding. In this case there is no reason to suppose that the syrinx was an unrelated "dysgenetic" lesion: it probably arose from ischæmic myelopathy.

List (1941) has commented on the difficulty in deciding, in some cases, whether dilatation of the central canal is a dysraphic malformation or due to obstructive hydromyelia (similar to obstructive hydrocephalis) caused by mechanical compression of the cord above the level of the lesion. In our Case 15 there was a spastic tetraparesis without spinothalamic sensory loss and at operation there was not only cerebellomedullary ectopia but also a cystic cervical cord. The ectopic tonsils were bound down to the cord by adhesions so that the circulation of the spinal fluid was probably impaired and the "cyst" in the cervical cord may have been an obstructive hydromyelia. In Case 21 there was a foraminal pressure cone and at operation a membrane was found, occluding the foramen of Magendie. Obstructive hydromyelia may well have been present in addition to the undoubted dysgenetic syringomyelia.

Russell and Donald (1935) found that hydromyelia was commonly present in the Arnold-Chiari malformation and that free communication between the ventricles and the spinal canal was not impeded. Gardner and Goodall (1950) reporting their operative findings in 17 cases of the "Arnold-Chiari malformation" stated that "the exposed portion of the cervical cord was cystic in 13 instances and in each case the fluid was clear and colourless." Eight of their cases also had cranio-vertebral anomalies.

### Cerebellar Ectopia in Patients with Cranio-Vertebral Anomalies: Its Relation to the Arnold-Chiari Malformation

We shall exclude from this discussion those cases in which slight "herniation" of the cerebellar tonsils is found at operation. Many such observations have been reported. O'Connell and Turner (1950) commenting on this finding in 3 of their 5 cases of basilar impression stated that it "was usually of the type associated with a rise of pressure in the posterior cranial fossa." We shall only consider cases in which displacement of the cerebellum into the cervical canal was a conspicuous feature and the cerebellar tissue was hypoplastic, poorly lobulated and malformed. In some of these cases the upper cervical roots take an upward course and the medulla is abnormal. The resemblance to the Arnold-Chiari malformation is then considerable.

Cerebellar ectopia may be encountered both with or without any skeletal cranio-vertebral anomaly and both in patients with spina bifida and meningocœle and in patients without such defects. There are four possible interpretations for these findings.

*Firstly*, the association of cerebellar ectopia with a lumbo-sacral meningocele has prompted the theory that the cerebellum is pulled into

the cervical canal during the period of growth, as the result of the tethering of the spinal cord or nerve roots at the site of the vertebral defect. *Secondly*, the cerebellum and brain-stem have been considered "pushed" into the cervical canal, as the result of increased pressure in the posterior fossa, the raised intracranial pressure being deemed a consequence of the cranio-vertebral anomaly. *Thirdly*, some would consider neither "traction" nor raised pressure the cause of the dislocation of the cerebellum, but believe that the abnormal position of the cerebellar tonsils merely reflects a foreshortening of the basiocciput or invagination of the rims of the foramen magnum. *Finally*, cerebellar ectopia may be regarded as a primary developmental defect, the tonsils actually developing ectopically. Their ultimate position is then not dependent upon either "traction," "pressure" or anomalous bony development.

(1) The "*traction*" theory, proposed by Lichtenstein (1942), is rejected by Russell (1949) for three reasons; (*a*) the absence of the Arnold-Chiari malformation from all cases of spina bifida occulta examined by her and from certain cases of lumbo-sacral meningocele where the spinal cord was tethered in the sacral region; (*b*) the presence of the malformation in association with spina bifida at a high level; (*c*) the absence of spina bifida in some of the reported cases. She could not confirm Lichtenstein's observation that in a case of the Arnold-Chiari malformation the brain-stem moved suddenly upward when the spinal cord was divided in the mid-cervical region. In only 1 of our 8 cases of cerebellar ectopia was a spina bifida demonstrated—and that at the C4 level.

(2) The "*pressure*" theory. Browne (1955) finds that "babies with the Arnold-Chiari malformation of the brain emerge from pregnancies in which the mother has had a very small abdomen, with very little liquor and abnormal discomfort." He believes that "excessive pressure would force the soft brain down through the foramen magnum like toothpaste out of a tube" (1953). Gardner and Goodall (1950) hold that the deformity of the hind-brain in these cases arises from simple foraminal herniation, the result of obstructive hydrocephalus originating in fœtal life.

We do not think these views can explain those cases where there is no evidence whatsoever of intracranial hypertension—as in 6 of our 8 cases. Neither can they account for the occasional *medullary* dislocation observed, nor for the upward course of the upper cervical roots. Moreover, many surgeons have commented on the fact that the displaced cerebellar tissue does not resemble the common cerebellar "pressure cone."

(3) This theory is suggested by Russell (1949). Speaking of basilar impression and associated skeletal malformations in the region of the foramen magnum she states that "foreshortening of the basi-occiput results in a dislocation of the brain-stem whereby the medulla and the cerebellar

XUM

tonsils are pushed into the upper cervical canal." She distinguishes this type of cerebello-medullary dislocation from the true Arnold-Chiari malformation and suggests that the latter term should be restricted "to those cases in which the spina bifida type of abnormality is identified."

We doubt, however, whether this hypothesis can account for more than a minority of cases showing both cerebellar ectopia and a skeletal defect at the cranio-vertebral junction. The extent of the cerebellar ectopia, in our experience, bears no relation to the degree of basilar impression or to the type of the other related skeletal abnormalities. Professor Russell's statement that "there is no evidence of any essential malformation of the neuraxis in such cases" does not take into account the association with true syringomyelia. We agree, however, that tonsillar ectopia in cases of *secondary* basilar impression resulting from Paget's disease (Ray, 1942) and osteogenesis imperfecta (O'Connell and Turner, 1950) may well be a direct outcome of the skeletal abnormality.

(4) We believe that the evidence indicates that the ectopic cerebellar tissue, in most cases, is neither "pushed" nor "pulled" through the foramen magnum. It is a malformation which may be unilateral or bilateral, of varying extent, and which may or may not be associated with skeletal defects at the cranio-vertebral junction or elsewhere in the spine. In our series there was no skeletal anomaly in Cases 19 and 20 and only minor anomalies in Case 21, yet cerebellar ectopia was a striking finding in each case. 2 of the cases with cerebellar ectopia also proved to have a syrinx at operation.

The original observations of Arnold and Chiari were made on infants; the cerebello-medullary malformation was associated with hydrocephalus and lumbo-sacral myelo-meningocele. It was for this group of cases that Schwalbe and Gredig (1907) coined the term "Arnold-Chiari malformation." The association with spina bifida can no longer be regarded as one of cause and effect. Experience has now shown that cerebellar ectopia may be found in adult life and that, as in the classical Arnold-Chiari malformation, it probably represents a primary developmental defect.

### Neurological Complications of the Klippel-Feil Syndrome

There was no neurological disability in the patient originally described by Klippel and Feil (1912) and no such complications were noted in Feil's thesis (1919), in Dubreuil-Chambardel's (1921) classical article or in Fischer's (1928) monograph. From a study of case reports and radiographs which have been published from time to time it is possible to say that when neurological complications do arise in the Klippel-Feil syndrome they are not directly due to the fused cervical vertebræ but to associated bony or neural malformations at the cranio-vertebral junction. Occipitalization of the atlas was present in the case of Rebierre (1923); occipitalization of the atlas, marked basilar impression, and subluxation

XUM

at C3–C4 and C4–C5 in the case of Guillain and Mollaret (1931); occipitalization of the atlas and an abnormally placed dens in the case of Baruch (1932); a malformed atlas with dislocated dens in the case of Laroche and Klotz (1933). The first of these four published cases had crossed lower cranial nerve palsies and the other three had spastic tetraparesis.

The published radiological data in certain other cases (Sicard and Lermoyez, 1923; Critchley, 1926; Cornil, 1928; du Toit, 1931; Latto, 1942); are not sufficient to permit critical comment but it is quite probable that in addition to the fusion of the cervical vertebræ there were also cranio-vertebral anomalies.

It is interesting also to note that in cases of the Klippel-Feil syndrome, an Arnold-Chiari type of malformation (Feller and Sternberg, 1932), an intraspinal cervical dermoid cyst (Dyke, 1947) and an extradural hæmangiolipoma (Bucy and Ritchey, 1947) have been reported.

Attacks of unconsciousness sometimes caused by sudden movements of the neck have been reported in patients with fused cervical vertebræ (Illingworth, 1956). Ford (1952) described recurrent syncope followed by vertigo, nystagmus and diplopia often related to head movements in a patient with atlanto-axial dislocations due to a hypoplastic odontoid.

## Summary

A clinical and radiological study is presented of 24 patients with congenital abnormalities in the region of the foramen magnum, causing neurological disability. Operation was performed in 8 cases.

*Radiological.*—The commonest bony anomaly of the cranio-vertebral junction, posterior spina bifida of the atlas, is of no clinical significance.

Basilar impression may be suspected when the odontoid process or the anterior arch of the atlas are found to occupy an unusually high position. Proof of its presence depends upon the demonstration, on the antero-posterior tomogram, of elevation of some part of the rim of the foramen magnum. Diagnosis solely from the lateral skull radiograph may involve errors. Isolated basilar impression is usually asymptomatic; a syringomyelic syndrome is the commonest clinical concomitant.

No case of platybasia was encountered in this series; it should not be confused with basilar impression. The differences between these two conditions are fully discussed. It is doubtful whether platybasia is of any clinical significance.

Occipitalization of the atlas may also be asymptomatic. It is likely to be associated with other skeletal anomalies at the cranio-vertebral junction and with neurological disability.

Chronic atlanto-axial dislocation resulting from a congenital defect is rare; it is particularly liable to cause spinal cord compression.

Fusion of cervical vertebræ is usually symptomless; the C2–C3 level is the commonest site of fusion. Patients with fused cervical vertebræ and

XUM

no other anomaly may develop tetraplegia following minor trauma. When chronic neurological disability is present, fusion of cervical vertebræ is probably never the sole anomaly; there is usually a bony defect at the level of the foramen magnum (basilar impression, occipitalization of the atlas or atlanto-axial dislocation).

*Clinical.*—Patients with cranio-vertebral anomalies often have short necks or some abnormality of posture of the head, especially if there is occipitalization of the atlas. Fusion of cervical vertebræ and basilar impression may be present in patients with necks of normal configuration. Certain stigmata are not uncommon; facial asymmetry; malformed ears; defective palates; congenital absence of thenar muscles; congenital absence of digits.

Anomalies of the cranio-vertebral junction are common in patients with syringomyelia. The relationship is rarely one of cause and effect; in the majority of instances the neural and skeletal defects are associated malformations; in the case of basilar impression the incidence of syringomyelia does not appear in any way related to the degree of skeletal abnormality or to its duration. Intramedullary cavitation in the cervical region may also arise from ischæmic myelopathy or obstructive hydromyelia.

Interesting signs that may be found in patients with cranio-vertebral anomalies are (1) postural loss confined to the upper limbs, (2) spontaneous vertical nystagmus (with oscillopsia), (3) mirror movements of the hands. Intracranial hypertension was rare in our cases.

Ectopia of the cerebellar tonsils or vermis is not uncommon in patients with skeletal malformations of the foramen magnum. It can also occur without such abnormalities and in the absence of spina bifida. In the majority of instances the cerebellar ectopia is developmental and not the result either of "traction" of the hind-brain through the foramen magnum or of "pressure" from above. Spontaneous vertical nystagmus was present in half the patients with cerebellar ectopia in this series. Whether such patients develop neurological signs may depend, to some extent, on the size of the foramen magnum (the foramen is often particularly large in these cases). Cerebellar ectopia may be demonstrated radiographically; a myelographic block is the rule; failure to fill the ventricles by lumbar air encephalography is common; the posteror inferior cerebellar artery, looping down into the cervical canal, may be visualized by vertebral angiography.

Not infrequently the surgeon discloses at operation lesions which are not suspected clinically, e.g. a cervical syrinx in a case with spinothalamic sensory loss; or cerebellar ectopia in cases without cerebellar signs. In other cases he may find that a syringomyelic syndrome is not accompanied by a cervical syrinx. Lastly, a dural band may be found with or without other anomalies, and may be responsible for some of the

XUM

disability. It is this diversity of the clinical picture and of the pathological findings at operation that makes it essential for each case to be studied on its own merits.

ACKNOWLEDGMENTS

We wish to thank Professor Lambert Rogers and Mr. Charles Langmaid, who operated on several of our patients, for their permission to refer to their operative findings. We are grateful to Mr. R. Marshall for the clinical photographs.

REFERENCES

AVERY, L. W., and RENTFRO. C. C. (1936) *Arch. Neurol. Psychiat., Chicago*, **36,** 1068.
BACHS, A., BARRAQUER-BORDAS, L., BARRAQUER-FERRÉ, L., CANADELL, J. M., and MODOLELL, A. (1955) *Brain*, **78,** 537.
BAGLEY, C., Jr., and SMITH, G. W. (1951) *Ann. Surg.*, **133,** 874.
BAKER, A. B. (1955) Clinical Neurology. London. Vol. III, p. 1678.
BARROWS, L. J., and COGAN, D. G. (1954) *Arch. Neurol. Psychiat., Chicago*, **72,** 116.
BARUCH, R. (1932) *Z. ges. Neurol. Psychiat.*, **139,** 462.
BAUMAN, G. I. (1932) *J. Amer. med. Ass.*, **98,** 129.
BAU-PRUSSAK, S., and FISZHAUT-ZELDOWICZ, L. (1938) *Rev. Neurol.*, **70,** 385.
BERG, F. T., and RETZIUS, A. "Museum Anatomicum Holmiensae." Fasc. I, Stockholm, 1855.
BERTOLOTTI, M. (1920) *Chir. Organi Mov.*, **4,** 395.
BOOGARD, J. A. (1865) *Ned. Tijdschr Geneesk.*, **1** (ii), 81.
BRAILSFORD, J. F. (1944) "The Radiology of Bones and Joints." 3rd edit. London.
BRAIN, W. R. (1955) "Diseases of the Nervous System." 5th ed. London.
BROWNE, D. (1953) *In* Garrod, Batten and Thursfield's "Diseases of Children". 5th ed. London, p. 260.
BROWNE, D. (1955) *Proc. R. Soc. Med.*, **48,** 850.
BUCY, P. C., and RITCHEY, H. (1947) *J. Neurosurg.*, **4,** 476.
BULL, J. W. D. (1946) *Proc. R. Soc. Med.*, **40,** 85.
—— (1951) *In* Feiling's "Modern Trends in Neurology." London, p. 600.
——, NIXON, W. L. B., and PRATT, R. T. C. (1955) *Brain*, **78,** 229.
CHAMBERLAIN, W. E. (1939) *Yale J. Biol. Med.*, **11,** 487.
CORNIL, L. (1928) *Rev. méd. Est.*, **56,** 525.
CRAIG, W. MCK., WALSH, M. N., and CAMP, J. D. (1942) *Surg. Gynec. Obstet.*, **74,** 751.
CRITCHLEY, M. (1926) *Brit. J. Surg.*, **14,** 243.
CUNNINGHAM, D. J. (1931) "Text-book of Anatomy." 6th ed. London.
CUSTIS, D. L., and VERBRUGGHEN, A. (1944) *Arch. Neurol. Psychiat.*, **52,** 412.
DEREYMAEKER, A. (1940) *J. belge Neurol.*, **40,** 575.
DUBREUIL-CHAMBARDEL, L. (1921) *Pr. med.*, **29,** 353.
DYKE, C. G. (1947) *In* Golden's "Diagnostic Roentgenology." New York.
EDWARDS, C. (1946) *Proc. R. Soc. Med.*, **40,** 87.
ELLIOTT, F. R., HUGHES, B., and TURNER, J. W. A. (1952) "Clinical Neurology." London.
ERSKINE, C. A. (1946) *Arch. Path.*, **41,** 269.
FEIL, A. (1919) L'absence et la diminution des vertèbres cervicales (étude clinique et pathogénique; le syndrome de la réduction numérique cervicale. Thèse de Paris.
—— (1921*a*) *Gaz. méd. Centre*, March.
—— (1921*b*) *Pr. méd.*, **29,** 515.
—— (1921*c*) *Pr. méd.*, **29,** *Annexes*, p. 860.



XUM

FELLER, A., and STERNBERG, H. (1932) *Virchows Arch.*, **285,** 112.
FISCHER, H. (1928) Les dysmorphies congénitales du rachis et leurs syndromes cliniques. Thèse de Bordeaux.
FISCHGOLD, H., and METZGER, J. (1952) *Rev. Rhum.*, **19,** 261.
FORD, F. R. (1952) *Bull. Johns Hopk. Hosp.*, **91,** 168.
GARCIN, R., and ŒCONOMOS, D. (1953) Les aspects neurologiques des malformations congénitales de la charnière cranio-rachidienne. Paris.
GARDNER, W. J., and GOODALL, R. J. (1950) *J. Neurosurg.*, **7,** 199.
GIRARD, P. F., RICARD, A., and DEVIC, M. (1949) *Rev. neurol.*, **81,** 229.
GRANT, J. C. B. (1940) "A Method of Anatomy." 2nd ed. London.
GUILLAIN, G., and MOLLARET, P. (1931) *Rev. neurol.*, **1,** 436.
GUSTAFSON, W. A., and OLDBERG, E. (1940) *Arch. Neurol. Psychiat., Chicago*, **44,** 1184.
GVOZDANOVIĆ, V., and DOGAN, S. (1951) *Acta radiol., Stockh.*, **35,** 124.
HOMÉN, E. A. (1901) *Dtsch. Z. Nervenheilk.*, **20,** 3.
ILLINGWORTH, R. S. (1956) *Arch. Dis. Childh.*, **31,** 8.
KLIPPEL, M., and FEIL, A. (1912) *Nouv. Iconogr. Salpét.*, **25,** 223.
LAROCHE, G., and KLOTZ, B. (1933) *Rev. neurol.*, **43** (ii) 47.
LATTO, D. (1942) *Brit. med. J.*, **1,** 669.
LICHTENSTEIN, B. W. (1942) *Arch. Neurol. Psychiat., Chicago*, **47,** 195.
LINDGREN, E. (1941) *Acta radiol., Stockh.*, **22,** 297.
LIST, C. F. (1941) *Arch. Neurol. Psychiat., Chicago*, **45,** 577.
MCGREGOR, M. (1948) *Brit. J. Radiol.*, **21,** 171.
MCRAE, D. L. (1953) *Acta radiol., Stockh.*, **40,** 335.
——, and BARNUM, A. S. (1953) *Amer. J. Roentgenol.*, **70,** 23.
MAYERSZKY, C. (1949) *J. Neurol. Neurosurg. Psychiat.*, **12,** 61.
MEIER, E. J. (1929) *Schweiz. Arch. Neurol. Psychiat.*, **24,** 303.
MERRITT, H. H. (1955) "A Text-book of Neurology." London. p. 386.
MEYER, B. C. (1944) *Arch. Neurol. Psychiat., Chicago*, **52,** 552.
MORETON, R. D. (1943) *Proc. Mayo Clin.*, **18,** 353.
O'CONNELL, J. E. A., and TURNER, J. W. A. (1950) *Brain*, **73,** 405.
PEYTON, W. T., and PETERSON, H. O. (1942) *Radiology*, **38,** 131.
PHILLIPS, D. G. (1955) *J. Neurol. Neurosurg. Psychiat.*, **18,** 58.
POPPEL, M. H., JACOBSON, H. G., DUFF, B. K., and GOTTLIEB, C. (1953) *Radiology*, **61,** 639.
QUAIN, J. (1882) "Anatomy." 9th ed. London.
RAY, B. S. (1942) *Ann. Surg.*, **116,** 231.
REBIERRE, P. (1923) *Pr. med.*, **31,** 452.
RECORD, R. G., and MCKEOWN, T. (1939) *Brit. J. Soc. Med.*, **3,** 183.
ROKITANSKY, C. (1846) "Lehrbuch der pathologischen Anatomie Wien. II. 149.
RUSSELL, D. S. (1949) *Spec. Rep. Ser. med. Res. Coun., Lond.* No. 265.
——, and DONALD, C. (1935) *Brain*, **58,** 203.
SAUNDERS, W. M. (1943) *Radiology*, **41,** 589.
SCHÜLLER, A. (1911) *Wien. med. Wschr.*, **61,** 2594.
SCHWALBE, E., and GREDIG, M. (1907) *Beitr. path. Anat.*, **40,** 132.

XUM

SCOVILLE, W. B., and SHERMAN, I. J. (1951) *Ann. Surg.*, **133,** 496.
SHOUL, M. I., and RITVO, M. (1952) *Amer. J. Roentgenol.*, **68,** 369.
SICARD, J. A., and LERMOYEZ, J. (1923) *Rev. neurol.*, **1,** 71.
——, and OBERTHUR (1904) *Rev. neurol.*, **12,** 899.
SMITH, C. K. (1947) *Amer. J. Dis. Child.*, **73,** 175.
SPIEGEL, E. A., and SCALA, N. P. (1944) *Arch. Otolaryng., Chicago*, **40,** 160.
SYMONDS, C. P., MEADOWS, S. P., and TAYLOR, J. (1937) *Brain*, **60,** 52.
DU TOIT, F. (1931) *Brain*, **54,** 421.
TOPINARD, P. (1895) "L'Anthropologie." Paris.
TÖRÖ, E. (1938) *J. exp. Zool.*, **79,** 213.
VIRCHOW, R. (1856) Gesammelte Abhandlungen zur wissenschaftlichen Medicin Frankfurt a/M. p. 969.
VIRCHOW, R. Med. Diss. Berlin, 1857. Quoted by Mayerszky (1939).
WALSH, M. N., CAMP, J. D., and CRAIG, W. MCK. (1941) *Proc. Mayo Clin.*, **16,** 449.
WILLARD, DEF. P., and NICHOLSON, J. T. (1934) *Ann. Surg.*, **99,** 561.
ZUCKERMAN, S. (1955) *Amer. J. Phys. Anthrop.*, **13,** 521.

## LEGENDS FOR PLATES

### PLATE III

CLINICAL

FIGS. 1 and 2 (*Case 13*).—Multiple skeletal anomalies of cranio-vertebral junction. Congenital absence of right thumb and malformation of the left thumb.

FIGS. 3 and 4 (*Case 16*).—Primary basilar impression with cerebellar ectopia. Low hair-line. Prominent ears.

FIG. 5 (*Case 17*).—(Post-operative). Basilar impression, occipitalization of atlas and fusion of dens to clivus. Short neck.

### PLATE IV

FIGS. 6 and 7 (*Case 20*).—Short neck. Cervical meningocele (operated) [*see* fig. 18]. Cerebellar ectopia.

FIGS. 8 and 9 (*Case 23*).—Klippel-Feil syndrome. Cervical meningocele (operated).

FIGS. 10 and 11 (*Case 24*).—Klippel-Feil syndrome.

### PLATE V

RADIOLOGICAL

FIG. 12 (*Case 10*).—Lateral tomogram. Odontoid and anterior arch of atlas lie above McGregor's line. Occipitalized posterior arch of atlas and fusion of C2–3.

FIG. 13 (*Case 11*).—Lateral tomogram. Anterior arch of atlas fused to clivus. No posterior arch identified. Marked atlanto-axial dislocation. The odontoid is beaked and protrudes into the posterior fossa.

FIG. 14 (*Case 11*).—Antero-posterior tomogram. Elevation of the rim of the foramen magnum. Only the right lateral mass of the atlas can be identified. The odontoid projects through the foramen magnum.

FIG. 15 (*Case 13*).—Lateral tomogram. Gross, multiple anomalies of the cranio-vertebral junction. Fusion of C2–C3 and of C4–C5–C6. Basilar impression. The anterior arch of the atlas can just be identified, high and unusually far forward. The posterior arch is occipitalized.

XUM

## PLATE VI

FIG. 16 (*Case 17*).—Lateral tomogram (post-operative.) Steep clivus in bony continuity with anterior arch of atlas and odontoid. The posterior arch of the atlas was occipitalized.

FIG. 17 (*Case 18*).—Necropsy specimen. Malformation of the hind-brain. Cerebello-medullary ectopia. Upward course of first cervical roots. The posterior arch of the atlas had grooved the left cerebellar tonsil. The brain had been tilted forward slightly to expose the low-lying left posterior inferior cerebellar artery.

FIG. 18 (*Case 20*).—Myelogram. Large foramen magnum and capacious upper cervical canal. Neck of meningocele outlined by contrast material.

XUM

XUM

XUM

PLATE III

FIG. 1.

FIG. 2.

FIG. 3.

FIG. 4.

FIG. 5.

*To illustrate article by John D. Spillane, Christopher Pallis and Arthur M. Jones,*

PLATE IV

FIG. 6.

FIG. 7.

FIG. 8.

FIG. 9.

FIG. 10.

FIG. 11.

*To illustrate article by John D. Spillane, Christopher Pallis and Arthur M. Jones.*

PLATE V

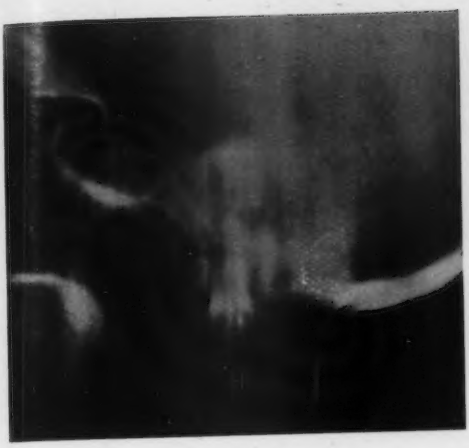

FIG. 12.

FIG. 13.

FIG. 14.

FIG. 15.

*To illustrate article by John D. Spillane, Christopher Pallis and Arthur M. Jones.*

XUM

PLATE VI

FIG. 16.

FIG. 17.

FIG. 18.

*To illustrate article by John D. Spillane, Christopher Pallis and Arthur M. Jones.*

XUM

XUM

# VASCULAR MECHANISMS OF BIRTH INJURY

BY

R. M. NORMAN, H. URICH AND W. H. McMENEMEY

*(From the Burden Mental Research Dept., Frenchay Hospital, Bristol, and the Maida Vale Hospital for Nervous Diseases, London)*

ALTHOUGH it is generally agreed that birth injury is responsible for at least some of the spastic and athetoid forms of cerebral palsy, much uncertainty exists as to the ways in which the underlying lesions have been brought about. The focal distribution of many of these lesions has suggested their vascular origin and, mainly on account of Schwartz's (1924, 1927) classical studies on birth injury, stagnant anoxia consequent upon venous engorgement has come to be regarded as the most important pathogenetic mechanism. This hypothesis finds its most plausible field of application in explaining the localization of those bilateral lesions of cerebral cortex, basal ganglia or centrum semiovale which lie within the drainage areas of the sagittal sinus or of the great vein of Galen. Less attention seems to have been paid to the role of the arterial system in the causation of birth injuries and its importance has probably been underestimated. Among the earlier writers on the subject Rydberg (1932) had expressed the view that intracerebral hæmorrhages were caused by sudden large fluctuations in arterial blood pressure, but he did not develop this theory to include the pathogenesis of such conditions as atrophic sclerosis of the cortex or ischæmic softening. More recently it has become evident that some of these later sequelæ of birth injury are more explicable on the basis of an arterial rather than a venous pathogenesis. J. E. Meyer (1953) has shown that cortical atrophic sclerosis (ulegyria) is often localized in the boundary zone lying between two main arterial territories. Another important principle is that displacement of the brain during birth (Earle, Baldwin and Penfield, 1953) may cause compression of arteries at certain preferential sites, just as may happen in conditions of raised intracranial pressure in later life (Lindenberg, 1955). Lesions attributable to these two types of vascular mechanism were present in the cases described in this paper and we believe that the analysis of the findings throws some light on the problem of the pathogenesis of cerebral birth injury.

*Case I.*—A. P., a male imbecile, was 28 years old at death.

*Clinical history* (An account of this patient's early days was given by his father).—He was the first-born, the other seven sibs being normal. The birth was said to have been difficult and prolonged and the mother had not been expected to survive. The

infant, who was "kept alive by his grandmother on drops of brandy," began to have fits within the first two weeks and these continued throughout life, averaging about three a month. He walked at 18 months and by the age of 6 years was recognized to be retarded mentally. When 15 he was certified as a mental defective. At this time he was unable to read, write or make simple calculations and had no initiative or sense of responsibility. There were no physical deformities or paralysis. He met his death by a self-inflicted stab wound of the heart.

### Examination of the Central Nervous System

*Macroscopic.*—The brain weighed 992 grammes of which the cerebellum accounted for 94 grammes. The frontal lobes were unduly small, the left being particularly reduced in size and showing severe shrinkage of the middle frontal gyrus. On coronal section it was seen that a zone of ulegyria occupied the anterior two-thirds of this convolution passing forwards to the frontal pole and arching downward into the orbital gyri. The affected areas showed severe shrinkage of the deeper parts of the gyral walls, the crowns being relatively preserved (Plate VII, fig. 1). Smaller patches of cortical atrophy were also found in the middle frontal and external orbital gyri of the right hemisphere (fig. 2). The cerebellum was atrophied in its anterior and inferior portion, the tonsil, biventral lobule and medial two-thirds of the inferior semilunar lobule being involved on the left side (fig. 3) while on the right only the tonsil was affected. The uvula and pyramid were the only affected parts of the vermis.

*Microscopic.*—Celloidin and frozen sections from representative parts of the cerebral cortex, basal ganglia, cerebellum and brain-stem were stained for nerve cells, myelin, fibrous neuroglia and lipid.

*Cerebral cortex:* The constricted basal parts of the atrophied convolutions were densely sclerosed, and showed almost complete destruction of nerve cells and fibres. In the better preserved "crowns" a patchy or sometimes pseudo-laminar loss of nerve cells was often associated with abnormal bundles or networks of fine myelinated fibres (*état marbré*) (fig. 4). The central cores of these gyri were largely devoid of myelin and sometimes contained small cavities. The cortical destruction was essentially focal in distribution, severely damaged areas lying side by side with normal or nearly normal tissue.

Sections passing through the left temporal pole showed an exceptionally dense marginal gliosis with numerous sheaf-like bundles of coarse astrocytic fibres. In the neighbouring grey matter there was a small wedge-shaped area of nerve cell loss, gliosis and overgrowth of myelinated fibres. The uncus itself was unaffected. No other lesions were found in the central, parietal, occipital or hippocampal regions of either hemisphere.

*Basal ganglia:* A severe loss of nerve cells with associated glial proliferation was present in the medial nucleus of the left *thalamus.* The left *amygdaloid nucleus* also showed a small area of atrophy. No pathological changes were seen in the *corpus striatum* and *globus pallidus* of either side, or in the right thalamus.

*Brain-stem:* The *mid-brain* and *pons* were normal. In the *medulla* the right inferior olive showed a mild loss of nerve cells in the lateral convolutions.

*Cerebellum:* Microscopical examination confirmed the extent of the atrophy already described. The cortex and central white matter of the left tonsil were completely atrophied, but elsewhere the pathological changes were less uniform and the crowns of the folia usually contained a few Purkinje cells and a sparse granular layer. The *dentate nuclei* were intact.

*Blood vessels:* No abnormality was seen in the pial, basal or intracerebral blood vessels.

XUM

*Case II.*—V. M., a female infant, was 10 months old at death.

*Family history.*—The patient was the youngest child of healthy parents. Two elder sibs are alive and well; the third, a premature baby weighing 3 lb. 9 oz., had died when a week old.

*Clinical history.*—The mother was 40 years old at the time of the patient's birth and had developed high blood pressure after the third month of pregnancy, but she did not suffer from headaches or visual disturbances. For three days prior to the onset of labour she was in hospital and there passed several small clots of stale blood *per vaginam.* The infant was born by left occipito-anterior presentation, the duration of the stages of labour being 8 hours, 10 minutes and 20 minutes respectively. There was a large retroplacental blood clot. The infant's birth-weight was only 3 lb. 8 oz. and an ulcerated area was present in the anterior frontal region of the scalp around which the blood vessels showed considerable dilatation. The baby's general condition aroused no special anxiety and she nearly always took her feeds well. At the age of 3 months she was discharged from the premature unit of the hospital, her weight then being 6 lb. 15 oz.

As time passed the mother noted that the infant did not make the same progress as her other children had done. She had to be fed by bottle and was never able to take even semi-solid food satisfactorily. She could move and raise her hands and kick vigorously but could never sit up without support nor grasp objects in the hands for more than a few seconds duration. Two weeks before her death she had her only recorded epileptic fit. Shortly before her death she was admitted to hospital with signs of an acute urinary infection. At that time her posture was one of opisthotonos and the limbs were spastic, the arms being more affected than the legs. There was irregular nystagmoid jerking of the eyes and the optic discs were reported to be pale. The cerebrospinal fluid was normal and not under increased pressure. Death was due to bronchopneumonia.

### Examination of the Central Nervous System

*Macroscopic.*—The left *cerebral hemisphere*: a large part of the fronto-parietal region was occupied by the thin membranous wall of a large porencephalic cyst (fig. 5). The defect involved the greater part of the third and much of the second frontal gyri, the outer half of the orbital surface of the frontal lobe, the lower two-thirds of the central convolutions and the inferior parietal lobule as far back as the angular gyrus. The temporal lobe appeared intact and the gyral pattern of the remainder of the left and right hemispheres was normal. On coronal section it was seen that the insula, external capsule, claustrum, the posterior half of the putamen and internal capsule had been destroyed. The left thalamus was markedly shrunken and sclerotic but showed no areas of softening. The *right hemisphere* also showed abnormalities on coronal section. The lateral ventricle was moderately dilated and the centrum semiovale narrowed. Close to the lateral angle of the lateral ventricle in the frontal and parietal regions the central white matter showed areas of discoloration suggestive of a spongy neuroglial scar. The *cerebellum* showed sclerotic atrophy of the semilunar lobules and there was a small area of cavitation in the depths of the horizontal fissure (fig. 6). In the *medulla* the left pyramid was greatly reduced in size.

*Microscopic.—Cerebral cortex:* The membranous roof of the porencephalic cyst was formed by leptomeninges and a thin layer of gliosed tissue probably representing the molecular layer of excavated and flattened convolutions. At the periphery the membrane was thicker and contained varying amounts of grey matter in the form of islands interspersed with bands of fibrous neuroglia. Many of the gyri at the margins of the cavity were club-shaped with densely sclerotic basal parts and relatively preserved crowns, the latter frequently showing hypermyelinated strands of fibres, perivascular

XUM

gliosis and narrow laminar or vertically arranged areas of nerve cell loss. Sometimes only half a gyrus had been preserved, its eroded side forming part of the wall of the main cystic cavity. The basal parts of the affected convolutions often showed small areas of old softening, walled by fibrous glia and containing groups of fat granule cells.

The temporal lobe on the side of the porencephaly was largely intact but a small focus of destruction was present in the wall of the middle temporal gyrus. A mid-cortical laminar loss of nerve cells accompanied by a glial scar was also found in the left superior temporal gyrus. The uncus and cornu Ammonis were unaffected and the remainder of the cortex in both hemispheres appeared normal.

*Central white matter:* In the left hemisphere dense fibrillary gliosis extended widely from the margins of the cystic cavity. In the otherwise well preserved white matter of the left temporal lobe a small area of incomplete softening was found in the anterior part of the ventricular wall. In this situation small aggregations of fat-granule cells were surrounded by a coarse lattice work of neuroglial fibres. A larger lesion of the same type was seen in the paraventricular region of the right frontal and parietal lobes (fig. 7).

*Basal ganglia:* The base of the porencephalic cyst was formed by remnants of the softened *putamen* which showed scattered fat-granule cells amid a dense gliomesodermal scar. The anterior part of the putamen was normal and the head of the *caudate nucleus* was also unaffected except for an enlarged zone of subependymal glial fibres and a few small patches of gliosis and nerve cell loss near the ventricular surface. The *globus pallidus* was intact. The left *thalamus* showed a widespread and severe loss of nerve cells and gliosis thoughout the lateral and medial nuclei. Many of the blood vessels in the medial nucleus were conspicuously ringed by dense aggregations of myelinated fibres which were in marked contrast to the otherwise very feebly myelinated tissue surrounding them (fig. 8). Bielschowsky staining confirmed the presence of numerous axis cylinders in these hypermyelinated zones. Holzer and Hortega preparations showed that, while an abnormal fibrous gliosis was present throughout these perivascular formations, the density of the fibrils was distinctly less than in the surrounding thalamic tissue. The blood vessels themselves were of normal structure and contained only scanty deposits of neutral fat in their cells.

The *right thalamus* showed a diffuse reduction in the number of nerve cells in its lateral nucleus. Severe and extensive changes were found in the *corpus striatum* of the right side which had largely lost its normal structure. Some of the large nerve cells and most of the smaller ones had disappeared from the central part of the putamen and had been replaced by an astrocytic gliosis and proliferated capillaries (fig. 9). In the *caudate nucleus* similar changes were seen and here an additional feature was the presence of numerous microglial cells containing flecks of neutral fat. These cells were especially evident in the head of the caudate nucleus where a great reduction in the numbers of both nerve cells and myelinated fibre bundles had taken place. Numerous fat droplets were present in the walls of the striatal vessels.

*Cerebellum:* In the superior semilunar lobules of either side only a few superficially situated folia had retained their normal granular layer and in these the Purkinje cells were reduced in number. Elsewhere in the depths of the sulci a complete atrophy of the parenchymatous elements had occurred with marked proliferation of the Bergmann astrocytes. The atrophied folia contained numerous ferruginated Purkinje cells. In the depths of the horizontal fissure the cortex had disintegrated, numerous fat-granule cells and a few encrusted Purkinje cells lying in a loose meshwork of neuroglia. Both *dentate nuclei* were extensively atrophied, the nerve cell loss and associated gliosis affecting the posterior and ventral convolutions. The cerebellar white matter showed loss of myelinated fibres only in the affected gyri and adjoining part of the centrum.

*Brain-stem:* The left pyramidal tract had completely degenerated. Many of the

nerve cells of the left nucleus pontis were smaller and stained poorly by comparison with those of the right and there was also a slight reduction in their numbers. The outer half of each inferior olive showed a substantial loss of nerve cells accompanied by marked fibrillary gliosis.

## Discussion

The clinical diagnosis of birth injury in both our cases, as in so many other retrospective studies, did not rest upon a very secure foundation. In the first case there was only the parent's statement that birth had been difficult, though certainly there appeared to be no post-natal illness to account for the child's subsequent disabilities. In the second case the points in favour of trauma having occurred were the low birth-weight and also the substantial retroplacental bleeding which might well have induced or aggravated a state of fœtal asphyxia. On the other hand, the congenital defect in the scalp, which appeared to be similar to the condition described by Greig (1931), was more suggestive of a prenatal anomaly. Nevertheless, the findings in these brains indicated with a high degree of probability that the damage had, in fact, occurred at birth. In the first place, no evidence of prenatal malformation of the brain was discovered, and secondly, the complex pattern of the cerebral destruction can be explained on the basis of vascular lesions due either to obstruction to individual blood vessels or to a generalized fall in systemic blood pressure. In the latter event the subsequent cerebral atrophy is characteristically localized to the boundary zones between two main arterial fields of supply. This phenomenon was first described by Lindenberg and Spatz (1939) in a non-arteriosclerotic obliterative disease of later life, considered by them to be a variant of Buerger's disease. Since then similar lesions have also been reported in conditions of generalized circulatory failure and in cases of birth injury (J. E. Meyer, 1953). The most commonly affected of the boundary zones is that lying between the middle and anterior cerebral fields of supply. In its maximal extent this area occupies a narrow strip of cortex reaching bilaterally from the parieto-occipital region along the middle frontal gyrus to terminate by arching downwards at the frontal pole to involve the orbital gyri. In our first case this fronto-orbital distribution was well exemplified, particularly on the left side. In our second case another boundary zone lesion had occurred between the territories of the superior and inferior cerebellar arteries. Here the atrophy had involved the superior and inferior semilunar lobules, and was most severe along the margins and in the depths of the horizontal fissure.

The pathogenesis of these boundary zone lesions is not fully understood except in the straightforward cases showing obliterative changes in the terminal vessels. Perhaps the most satisfactory explanation is to be found in the effect of low systemic blood pressure upon the cerebral circulation. Thus the blood supply may be presumed to be adequate for the proximal but not for the distal territories. This concept of "the last field" in an

XUM

irrigation system (Zülch, 1954) does not, however, account for all of the peculiarities of the boundary zone phenomenon. For instance, the orbital surface of the frontal lobe may be more severely damaged than the considerably more distal parietal area. Whatever the precise mode of origin of these lesions may be, their presence in cases of birth injury is not surprising. Anoxia, if sufficiently severe, ultimately leads to sudden circulatory collapse, as had been shown in the animal experiments of Noell and Schneider (1942). Circulatory failure, as evinced by "white asphyxia," is a well-known accompaniment of birth trauma and Gruenwald's (1955) observations on the syndrome of perinatal distress have emphasized the importance of the factor of neonatal shock.

In addition to these boundary zone lesions, both our cases showed areas of cortical damage which corresponded wholly or in part to the territories of individual arteries. In Case I, the cerebellar atrophy occupied that portion of the inferior surface lying within the distribution of the lateral branches of the posterior inferior cerebellar arteries. On the left side the lesions affected the whole of this vessel's territory, while the more limited area of destruction on the right side also lay within the same arterial fields. Variations of this sort are to be expected and depend upon the efficacy of the anastomoses with neighbouring vessels (Van der Eecken and Adams, 1953). Thus the massive softening of the left cerebral hemisphere in Case II occupied the complete field of the middle cerebral artery except for the superior and middle temporal gyri which were substantially unaffected, presumably because of the anastomoses with branches of the posterior cerebral artery.

Occlusion of major arteries occurring in the paranatal period has most commonly been ascribed to embolism (Hallervorden, 1937; Clark and Linell, 1954) and changes in the vessel wall suggesting recanalized thrombus have been found in several cases (J. E. Meyer, 1951). In the present cases the blood vessels appeared normal, though a meticulous search along the length of the arteries in question was not attempted. It appears probable that the observed lesions were the result of arterial compression occurring at the time of birth. Lindenberg (1955) has recently brought forward abundant evidence that compression of arterial trunks or branches against rigid structures may take place in any condition associated with increased intracranial pressure and displacement of the brain. Cerebral distortion during the passage of the fœtal head through the birth canal may also lead to similar vascular lesions. Among the first to realize this positively were Earle, Baldwin and Penfield (1953) who pointed out that herniation of the uncus at birth might compress the anterior choroidal artery and branches of the posterior cerebral artery against the edge of the tentorium and so lead to temporal lobe sclerosis. It is obvious that compression of arterial trunks would be greatly facilitated by a fall in systemic blood pressure and it appears to be a fact of considerable significance that

in both our cases lesions attributable to arterial obstruction coexisted with lesions of the boundary zones. The cerebellar atrophy in the first case may thus be regarded as the sequel of compression of the lateral branches of the posterior inferior cerebellar arteries against the rim of the foramen magnum—one of the preferential sites of occlusion according to Lindenberg. The large area of softening in the left cerebral hemisphere in Case II is, however, not so easily explained. Lindenberg has shown that the middle cerebral artery may be compressed as it passes round the limen insulæ, but in our case the lenticulo-striate branches must also have suffered. It may well be that we are dealing here with an obstruction of the internal carotid itself situated at its vulnerable point of emergence from the cavernous sinus. Support to this view is given by one of the cases of cerebral infarction described by Adams (1954) in which occlusion of the internal carotid had led, in the context of certain associated abnormalities of anastomotic supply, to a pattern of lesions closely resembling that seen in our second case.

In contrast to the findings recorded above, the paraventricular softening present in the right cerebral hemisphere in Case II may best be understood as the consequence of obstruction to the venous side of the circulation. The classical work of Schwartz (1924, 1927) has amply demonstrated that widespread necrosis of the centrum semiovale is often associated with hæmorrhage into the head of the caudate nucleus or into other parts of the basal ganglia, drained by the tributaries of the great vein of Galen. In several examples of residual birth injuries found in older patients suffering from cerebral palsy similar paraventricular lesions have been interpreted as the consequences of congestion and stasis in the distribution of the anterior terminal vein (Norman, 1944, 1947, 1949). There seems no good reason for departing from this theory of a venous pathogenesis in the present instance, for although these softenings also lay within the boundary zone of the anterior and middle cerebral arteries, they were not accompanied by atrophy of the overlying middle frontal gyrus. Moreover, a smaller paraventricular softening of precisely similar histological appearance was present in the white matter of the left temporal lobe which is drained by the choroidal branch of the internal cerebral vein. Holland (1920, 1922) showed that if the tentorium is pulled upwards by the falx, as occurs when the vertical diameter of the fœtal skull is unduly increased, the great vein of Galen may be torn at its junction with the straight sinus. It would seem probable that with less severe distortion of the head, kinking and temporary obstruction of the vein may occur, leading to engorgement or hæmorrhages in the field of drainage. This explanation of the Galenic distribution of many of the lesions of birth injury is more convincing than the complicated theory of pressure differences put forward by Schwartz and is certainly more applicable to the present cases where distortions of the brain substance had evidently occurred.

XUM

The atrophy of the lateral nucleus of the right thalamus in Case II also belongs to this picture of Galenic stasis since in view of the intact cerebral cortex of this hemisphere the cell loss cannot be ascribed to retrograde changes. The lesions of the neighbouring putamen and caudate nucleus appeared to be of more recent origin because of the microglial activity still present in the areas of atrophy. These changes may perhaps be related to the fit which the patient experienced a fortnight before death, and such an explanation would be in harmony with the theory of post-epileptic brain damage put forward by Scholz (1951). It is tempting, though purely conjectural, to postulate some predisposing factor initiated by birth injury which had rendered these centres specially vulnerable. This possibility has been suggested to us by Courville's (1953) writings on the subject of the late sequelæ of cerebral anoxia.

Finally, brief mention may be made of the peculiar aggregations of myelinated fibres present around some of the thalamic blood vessels in our second case. These dense clear-cut collars differed strikingly from the more usual picture of diffuse fibre networks seen in *état marbré* in the thalamus or corpus striatum. They cannot well be regarded as preserved islands of normal tissue since their density of myelination is foreign to the medial nucleus of the thalamus which normally is very lightly myelinated. Somewhat similar whorls of fibres were seen by Wertham (1934) in a demyelinated area in the cerebellum in a case of diffuse sclerosis and were considered by the author to be regenerated nerve fibres. It is also well known that regenerated axons after injury to the spinal cord often favour a perivascular course (Druckman and Mair, 1953). It may therefore be suggested that in our case a post-natal growth of axis cylinders had followed the line of the neighbouring blood vessels, perhaps as the expression of a true regenerative process, perhaps as a hypertrophy of the collateral branches of injured axons as described by Cajal (1928). These new fibres later acquired myelin sheaths which, in the mass, have given the perivascular structures their appearance of hypermyelination.

## Summary

A description has been given of the clinical and pathological features of two cases of mental deficiency apparently caused by injury at birth. Both brains showed areas of cortical atrophy in the cerebrum and cerebellum occupying either the boundary zone between two main arterial territories or lying within the fields of supply of individual arteries. These cases illustrate the complex interplay of the vascular mechanisms operative in cerebral birth injury. The boundary zone lesions were considered to be due to a fall below critical level in the systemic blood pressure such as might have occurred in shock associated with birth injury. The second type of lesion was believed to have followed compression of arteries at certain preferential sites caused by the displacement of the brain substance

XUM

during the process of birth. Such compression would be facilitated by a coincidental lowering of blood pressure and it is significant that in these brains, lesions of both types of distribution occurred together. In the second case, paraventricular softenings of the central white matter and pathological changes in the basal ganglia formed a pattern of cerebral damage attributable to obstruction of the great vein of Galen. In addition, the medial thalamic nucleus contained dense perivascular rings of myelinated fibres which differed from the appearances hitherto reported in *état marbré*.

We are indebted to Dr. R. D. Clay, of the Portsmouth and Isle of Wight Area Pathological Service, for allowing us to investigate Case I.

We wish to thank Dr. Beryl Corner for her kind permission to use her hospital records of Case II.

This work was carried out with the assistance of the Nuffield Foundation.

## REFERENCES

ADAMS, R. D. (1954) *J. Neuropath.*, **13,** 1.

CLARK, R. M., and LINELL, E. A. (1954) *J. Neurol. Neurosurg. Psychiat.*, **17,** 295.

COURVILLE, C. B. (1953) "Contributions to the Study of Cerebral Anoxia." Los Angeles.

DRUCKMAN, R., and MAIR, W. G. P. (1953) *Brain*, **76,** 448.

EARLE, K. M., BALDWIN, M., and PENFIELD, W. (1953) *Arch. Neurol. Psychiat., Chicago*, **69,** 27.

GREIG, D. M. (1931) *Edinb. med. J.*, **38,** 341.

GRUENWALD, P. (1955) *Arch. Path.*, **60,** 150.

HALLERVORDEN, J. (1937) *Med. Klinik*, **33,** 1224.

HOLLAND, E. (1950) *Trans. Edinb. obstet. Soc.*, **40,** 112.

—— (1922) *J. Obstet. Gynæc., Brit. Emp.*, **29,** 549.

LINDENBERG, R. (1955) *J. Neuropath.*, **14,** 223.

——, and SPATZ, H. (1939) *Virchows Arch.*, **305,** 531.

MEYER, J. E. (1951) *Arch. Psychiat. Nervenkr.*, **186,** 437.

—— (1953) *Arch. Psychiat. Nervenkr.*, **190,** 328.

NOELL, W., and SCHNEIDER, M. (1942) *Pflüg. Arch. ges. Physiol.*, **246,** 181.

NORMAN, R. M. (1944) *Arch. Dis. Childh.*, **19,** 111.

—— (1947) *J. Neurol. Neurosurg. Psychiat.*, **10,** 12.

—— (1949) *Brain*, **72,** 83.

RAMON Y CAJAL, S. (1928) "Degeneration and Regeneration of the Nervous System." London. Vol. 2.

RYDBERG, E. (1932) *Acta path. microbiol. scand.*, Suppl. 10.

SCHOLZ, W. (1951) "Die Krampfschädigungen des Gehirns." Berlin.

SCHWARTZ, P. (1924) *Z. ges. Neurol. Psychiat.*, **90,** 263.

—— (1927) *Ergebn. inn. Med. Kinderheilk.*, **31,** 165.

VANDER EECKEN, H. M., and ADAMS, R. D. (1953) *J. Neuropath.*, **12,** 132.

WERTHAM, F., and WERTHAM, F. (1934) "The Brain as an Organ." New York, p. 336.

ZÜLCH, K. J. (1954) *Dtsch. Z. Nervenheilk.*, **172,** 81.

XUM

## LEGENDS FOR PLATES

### PLATE VII

FIG. 1 (*Case* 1).—Coronal sections of left cerebral hemisphere to show scarring of middle frontal gyrus with loss of myelin. (Loyez.)

FIG. 2 (*Case* 1).—Coronal section of right cerebral hemisphere showing a less marked degree of atrophy and an *état marbré* of the middle frontal gyrus. (Loyez.)

FIG. 3 (*Case* 1).—Left cerebellar hemisphere showing localized cortical atrophy in antero-inferior part. (Nissl.)

FIG. 4 (*Case* 1).—Lateral surface of anterior part of left frontal lobe showing extensive *état marbré* of cortex. (Loyez.)

FIG. 5 (*Case* 2).—Fronto-parietal porencephalic cyst of left hemisphere.

FIG. 6 (*Case* 2).—Cerebellum showing localised atrophy of cortex with a cavity in the depth of the horizontal fissure. (Loyez).

### PLATE VIII

FIG. 7 (*Case* 2).—Softening in the white matter of the right hemisphere adjacent to the ventricle. (Loyez.)

FIG. 8 (*Case* 2).—Median nucleus of left thalamus showing blood vessels ringed with myelin. (Loyez.)

FIG. 9 (*Case* 2).—Right putamen. There is loss of nerve cells with astrocytic gliosis and proliferation of capillaries. (Hæmatoxylin and eosin.)

XUM

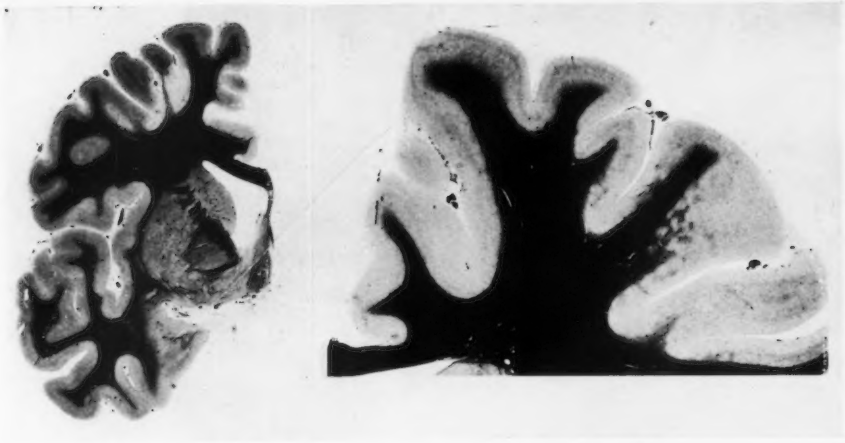

FIG. 1. FIG. 2.

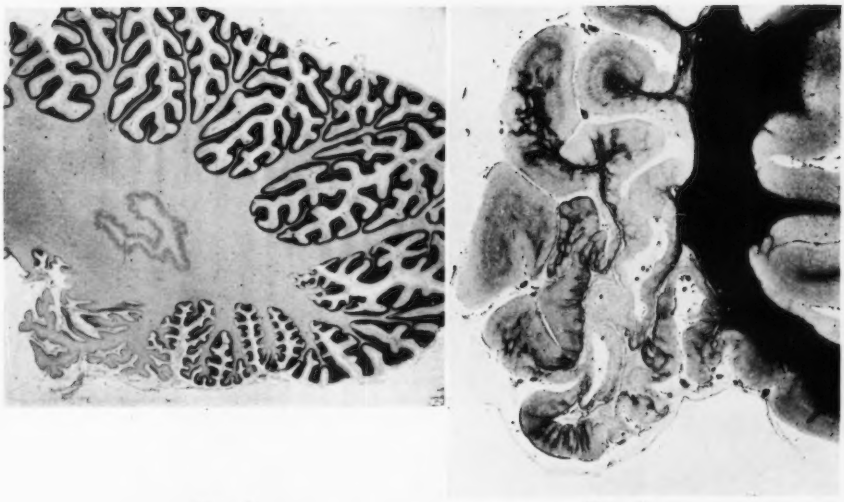

FIG. 3. FIG. 4.

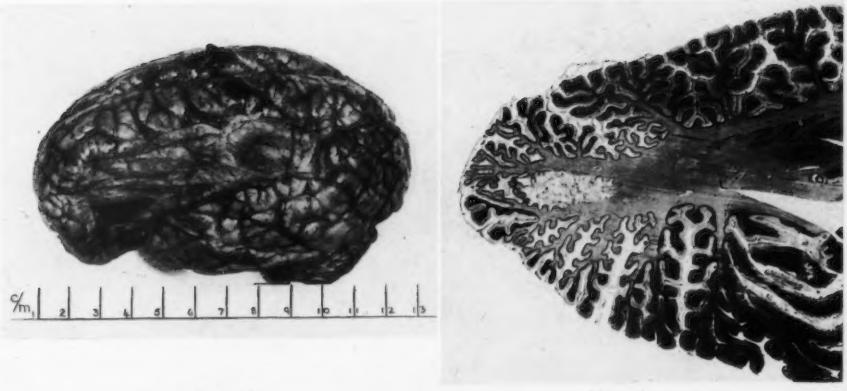

FIG. 5. FIG. 6.

*To illustrate Article by R. M. Norman, H. Urich and W. H. McMenemey.*

XUM

PLATE VIII

FIG. 7.

FIG. 8.

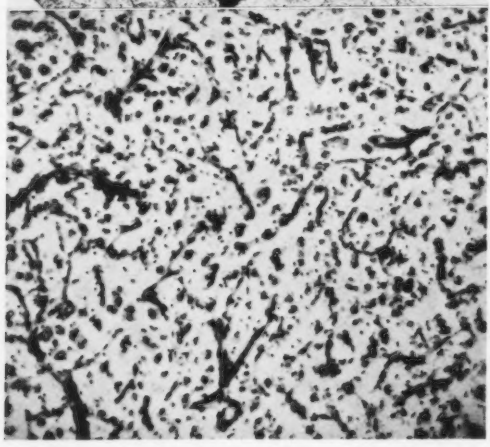

FIG. 9.

*To illustrate article by R. M. Norman, H. Urich and W. H. McMenemey.*

# BEHÇET'S SYNDROME WITH NEUROLOGICAL COMPLICATIONS

BY

NOSHIR WADIA AND EIRIAN WILLIAMS

*(From the London Hospital, E.1)*

AN association between oral and genital ulceration and hypopion iritis has been observed for many years (Planner and Remenovsky, 1922; Adamantiades, 1931) but its recognition as a specific syndrome or disease entity is due mainly to Behçet (1938, 1939), who gave a detailed clinical description of 5 cases. Several reports and reviews have since appeared, notably those of Curth (1946), Berlin (1944), France *et al.* (1951) and Phillips and Scott (1955) and features other than the original "triple symptom complex" are now recognized.

Involvement of the nervous system, although rare, is a serious complication which has been responsible for the three recorded deaths, but the diagnosis of Behçet's syndrome in such cases will clearly be missed unless its commoner manifestations are sought and recognized.

The illness is recurrent in nature, with attacks three or four times a year (Behçet, 1938) or more or less frequently; and the mouth, genitalia and eyes may be affected separately or together. The ulcers in the mouth sometimes extend into the pharynx and œsophagus but Behçet's claim that they differed in appearance from ordinary aphthæ has not been upheld by subsequent authors. Thus France *et al.* (1951) found them to be indistinguishable, except when they started as submucous nodules, or when two or more would coalesce to form a single large irregular lesion. They tend to appear in crops, and vary in size from a few millimetres to a centimetre or more in diameter, each ulcer persisting for days or weeks according to its size. It often has a dusky red areola and is intensely painful, sometimes interfering with speech and nutrition.

The genital ulcers are larger, up to 5 cm. diameter (Phillips and Scott, 1955), and although usually painful they are not invariably so (Gray, 1950). They are found on the perineum and cervix as well as on the vulva in the female, may lead to fenestration of the labia minora, and heal with considerable scarring. Similar lesions in the male occur on the penis and scrotum (Berlin, 1944).

Ocular involvement is at first unilateral, but with repeated attacks

XUM

sight in both eyes may be seriously impaired. The commonest lesion in the eye is hypopion iritis; but conjunctivitis, keratitis, retinitis, retrobulbar neuritis, retinal hæmorrhage, and thrombophlebitis are not rare. Intense pain is a distressing symptom which, with blindness, may call for enucleation (Thomas, 1947).

Skin lesions are common. In 31 cases reviewed by France *et al.* (1951) erythema nodosum was present in 11, pyoderma in 15 and a non-specific skin sensitivity, previously observed by Katzenellenbogen (1946) in 7. In only 11 was the skin normal. Acneiform and pustular lesions when scanty are easily overlooked, but, on the other hand, large indolent and intractable ulcers may be found (Pallis and Fudge, 1956).

Thrombophlebitis of small or large veins occurs in 25 per cent of cases (France *et al.*, 1951) but although muscle and joint pain is common, obvious joint swelling is rare. Fever, lassitude and malaise may also be present during the more acute phases of the illness.

Those cases with neurological complications have recently been reviewed by Pallis and Fudge (1956), and we now record three further examples before discussing this aspect in greater detail.

*Case* 1.—A female shop assistant aged 16 years. (L.H. No. 24426/55.) Admitted on 16.7.55.

For three months she had complained of recurrent painful ulceration of the mouth and vulva, with "spots" mainly on the face and limbs. She had also felt tired and unwell, and had lost 2 st. in weight.

Three weeks before admission her right eye became intensely painful with photophobia and blurring of vision. These symptoms subsided in a few days to recur on the day of admission.

Frontal headache, aching pains in the calves and "pins and needles" in the feet had been present for a week.

She had previously been healthy but her family history was of interest. Her paternal grandfather and an aunt had died of tuberculosis and her brother during childhood had been treated for abdominal tuberculosis.

On examination she was febrile (T.100° F.), ill and unhappy. There were many pustules and acneiform lesions on her back and limbs and a tender erythematous nodule (0·5 cm. diameter) was found on the left shin. Her mouth contained small, painful ulcers, mainly on the lips and tongue. Her right eye was inflamed due to iridocyclitis, with ciliary injection, posterior synechiæ and a vitreous haze, but her left eye was normal.

*Investigations.*—Hæmoglobin was 83 per cent, white count 10,600 with a normal differential count and erythrocyte sedimentation rate 25 mm. in one hour. Mantoux test 1:100 was positive. Other investigations which proved negative included Paul Bunnell and Widal reactions, toxoplasma dye and complement-fixation tests, and radiographs of chest and skull. Plasma proteins were normal, albumin 5·0 grammes per 100 ml., globulin 2·8 grammes per 100 ml. and fibrinogen 0·31 grammes per 100 ml.

C.S.F. (culture for tubercle bacilli—negative).

| | *Pressure* (*mm. water*) | *Cells* (*per c.mm.*) | *Protein* (*mg./100 ml.*) | *Sugar* (*mg./100 ml.*) | *Chloride* (*mg./100 ml.*) |
|---|---|---|---|---|---|
| 19.7.55 | 70 | 24<br>Mainly lymphocytes | 40 | 63 | 602 |
| 22.7.55 | 90 | 59<br>Mainly lymphocytes | 50 | 71 | 620 |
| 6.8.55 | 200 | 126<br>70% lymphocytes<br>30% polymorphs | 90 | 48 | 580 |
| 16.8.55 | 130 | 90<br>Mainly lymphocytes | 130 | 50 | 614 |
| 3.11.55 | 70 | 22<br>Lymphocytes only | 40 | 63 | 750 |

*Progress.*—On the fourth day of admission slight neck rigidity was detected and a diagnosis of tuberculous meningitis was considered. In spite of treatment with Marsalid (isopropyl-isonicotinic acid hydrazide) 100 mg. t.d.s. and streptomycin 1 gramme I.M. daily her headache remained with vomiting two or three times daily, and she also complained of severe back pain. The right iridocyclitis which initially became more severe had improved slightly, but bilateral papillœdema was now present.

During the second week of admission two painful ulcers (0·5 cm. diameter) appeared on the vulva on contiguous surfaces of the labia majora. Both healed within two weeks and apart from the persistence of oral ulceration, fever and papillœdema, her condition began to improve. The diagnosis was now changed to that of Behçet's syndrome.

On 13.9.55 in the ninth week of admission, the iridocyclitis in the right eye suddenly flared up again, and in spite of marked vitreous haze involvement of the retina could be seen in the form of several greyish exudates mainly near the disc. Visual acuity was markedly reduced. At the same time bilateral pyramidal signs appeared in the form of brisk limb reflexes, knee and ankle clonus, absent abdominal reflexes and extensor plantar responses.

The antituberculous drugs had meanwhile been discontinued, penicillin and erythromycin had been found to be equally ineffective and on 26.10.55 oral cortisone 25 mg. six-hourly was commenced. Cortisone 10 mg. had already been given by subconjunctival injection with slight benefit.

Her progress on cortisone by mouth was impressive. Signs of acute iritis and retinitis regressed rapidly and within three weeks there was only slight haziness of the right vitreous. Her general condition also improved.

She was discharged receiving cortisone 50 mg. later reduced to 25 mg. daily. Ulcers have continued to appear in the mouth at infrequent intervals, but there has been no recurrence of lesions on the genitalia. Vision in the right eye is still impaired 6/60, left 6/6, abdominal reflexes are absent and plantar responses extensor.

*Comment.*—Acute meningoencephalitis with headache, neck stiffness, bilateral papillœdema and pyramidal signs in a girl complaining of ulcers in the mouth and vulva. Two attacks of iridocyclitis occurred during her admission. A diagnosis of tuberculous meningitis was at first considered and the patient improved finally on treatment with cortisone.



XUM

*Case* 2.—A fitter aged 40 years. (L.H. No. 43122/54.)

Admitted on 13.5.56.

Five years previously he had complained of small painful ulcers in his mouth which had since recurred periodically. At the same time his eyes were bloodshot on several occasions and he also complained of night sweats and fever for three months.

Three years before admission a painful scrotal ulcer appeared, which healed spontaneously after a few weeks and was followed by others over the next six months. Small red spots on his wrists, back and thighs looked at first "like boils" but always faded without suppurating. He began to suffer from occipital and frontal headaches, lost interest in his work and home, became depressed with fits of crying, and his personal habits deteriorated. He was sometimes incontinent of fæces and there was complete loss of libido. In November 1954 he was admitted with a diagnosis of organic dementia due to disseminated sclerosis. During the previous six weeks he had complained of persistent diplopia but no abnormality was found to account for it. On lumbar puncture the cerebrospinal fluid pressure was 185 mm. water, with cells 19 per c.mm. (lymphocytes only) and protein 60 mg. per 100 ml. The Wassermann reaction was negative and Lange curve normal. An electro-encephalogram performed on 13.1.55 was diffusely abnormal, slightly more so on the left, and compatible with widespread, possibly mild, cerebral damage.

He subsequently attended the Psychiatric Outpatient Department and progressive mental deterioration was noted.

Six months and two months before his present admission he again complained of diplopia which persisted for a few weeks on each occasion, for two months he had experienced difficulty with micturition and unsteadiness on walking, and for one month ulcers had been present in his mouth. There was no relevant past or family history.

On examination he was a well-nourished man with severe dementia. A few acneiform lesions were found on his back and chest. There were two small ulcers on the tongue (Plate IX, fig. 1) and scars of healed ulcers on the scrotum (fig. 2). Marked intellectual impairment with loss of memory for recent events became apparent on simple questioning, and he had no insight into his condition. He showed marked emotional lability and euphoria and pathological laughter could easily be induced. His face, at other times, was expressionless and his speech was grossly slurred.

The right pupil was smaller than the left, both reacting to light and accommodation, and other abnormal findings included weakness of upward gaze, spasticity of the jaw, face and tongue, with a brisk jaw-jerk. The palate moved weakly. There was slight weakness of the right arm and leg with increased tone in all four limbs, reflexes were grossly exaggerated, right more than left, abdominals absent and plantar responses extensor. His gait was unsteady but no abnormal sensory signs were discovered. There was no neck stiffness.

*Investigations.*—Hæmoglobin 92 per cent, white cells 14,000 per c.mm. with a normal differential count. E.S.R. 10 mm. in one hour. Lumbar puncture was performed on 14.5.56. The cerebrospinal fluid pressure was 130 mm. water with cells 20 per c.mm. (lymphocytes only), protein 60 mg. per 100 ml., sugar 65 mg. per 100 ml. and chlorides 742 mg. per 100 ml. Culture was sterile, the Wassermann reaction negative and Lange curve normal. Other investigations which proved negative were Mantoux test 1/100, toxoplasma dye and complement-fixation tests, complement-fixation test for lymphogranuloma venereum, Frei test and Dmelcos test. The plasma fibrinogen was 0·3 grammes per 100 ml., albumin 4·5 grammes per 100 ml., and globulin 2·4 grammes per 100 ml.

*Progress.*—Cortisone 25 mg. t.d.s. was commenced during admission without apparent benefit, except that the mouth ulcers disappeared. When seen a month later in the outpatients' department, a fresh crop of ulcers was noted, and his pyramidal and bulbar signs were more marked.

PLATE IX

XUM

XUM

FIG. 1.—Ulcers on the tongue in Behçet's syndrome.

FIG. 2.—Scars of scrotal ulcers in Behçet's syndrome.

*To illustrate article by Noshir Wadia and Eirian Williams.*

*Comment.*—Progressive dementia, recurrent diplopia and pseudobulbar palsy with features of Parkinsonism in a man complaining of recurrent oral and genital ulceration. He gave a doubtful history of eye disease.

*Case* 3.—A publican's wife aged 41 years. (L.H. No. 39013/54.)

Admitted on 14.3.56.

Five years previously she had complained of blurring of vision in the right eye attributed by an ophthalmologist to retinitis. It persisted in spite of gingivectomy for oral sepsis, and retro-orbital injections of cortisone a year later were also without effect.

Two and a half years before admission vision in the left eye became impaired, and because of bilateral disc œdema a diagnosis of intracranial tumour was considered. All investigations including lumbar puncture, air encephalography and electroencephalography were negative, however, and her eyes gradually improved. A year later she complained of painful swelling of both knees followed within a month by swelling of the index and middle fingers of the left hand. She was admitted to hospital (25.10.54) with a diagnosis of rheumatoid arthritis. Effusions were present in both knees, there was active uveitis involving both eyes, with aqueous flare, cells in the anterior chamber and haziness of the vitreous. Dilated veins and a small hæmorrhage were seen on the retina of the right eye. Visual acuity right 6/36, left 6/24. Her hæmoglobin was 70 per cent, white blood count 12,200 with normal differential and E.S.R. 91 mm. in one hour. Hydrocortisone 75 mg. was injected into the right knee and cortisone drops were instilled into both eyes with no benefit. She was discharged receiving cortisone by mouth 25 mg. twice daily, but bilateral uveitis persisted as did the effusions into the right knee.

Seven weeks before admission while still receiving cortisone she complained of severe vertical and frontal headache for one day, with retching and vomiting, and three days later was found to have course nystagmus and dissociated ocular movements. Lateral movements were full, vertical movements absent and her left eye deviated inwards on attempting to look down. Ocular movements returned to normal within a month.

On admission for further investigation a history of recurrent oral and vulval ulceration was elicited for the first time. For four years painful ulcers had been appearing in her mouth, three or four at a time and at six to eight week intervals. Larger ulcers had twice appeared on the vulva, four or five on each occasion, causing irritation but no great pain.

On examination her right knee was swollen but her joints were otherwise normal and no ulcers or scars were present in the mouth or on the vulva. There were signs of bilateral chronic uveitis and reduction of visual acuity (right counting fingers, left 6/36). The left disc was swollen. There was no nystagmus and external ocular movements were full. The rest of the nervous system was normal.

On lumbar puncture the cerebrospinal fluid pressure was 140 mm. water, with cells 3 per c.mm. and protein 20 mg. per 100 ml. The Wassermann reaction was negative and Lange curve normal. X-rays of chest and skull were also normal. Total plasma proteins were 6·0 grammes per 100 ml. and plasma fibrinogen 0·3 grammes per 100 ml. Her hæmoglobin was 61 per cent, colour-index 0·66, and white cells 14,800 with a normal differential count.

*Progress.*—Three months later she was admitted elsewhere with a large ulcer on the vulva.

XUM

*Comment.*—Acute encephalitis presenting with headache, nystagmus, dissociated ocular movements and loss of upward gaze in a woman with bilateral uveitis. Recurrent ulcers of the mouth and vulva were also present. Bilateral papillœdema at one stage suggested a diagnosis of intracranial tumour.

## Discussion

The first example of Behçet's syndrome with neurological complications was recorded by Knapp (1941) and nine others have since been described. We reject one case described by Chauffard *et al.* (1923) and another by Thomas (1947) because in neither was there sufficient evidence of nervous system involvement; and we also exclude Silfverskiöld's second case (1951) where the diagnosis is in doubt. This patient presented with choroidoretinitis and paraplegia, but without genital or oral ulceration, and while we agree with Curth (1946) that the presence of two of the three classical signs is sufficient grounds for diagnosis, as in our Case 2, it cannot reasonably be made when only one of these is present.

Of the 13 cases, which include our own, 5 have been females and 8 males, their ages ranging from 16 years to 47. Other symptoms of Behçet's syndrome have in all of them preceded those referable to the nervous system, the diagnosis in our experience being made only when the significance of these other symptoms was recognized.

The 10 previously recorded cases are summarized below and it can be seen that although the clinical picture is variable with symptoms suggesting widespread involvement of nervous tissue, some of these symptoms are commoner than others. Pallis and Fudge (1956) have gone so far as to differentiate three main neurological syndromes: (1) a brain-stem syndrome, (2) a meningomyelitic syndrome, and (3) an organic confusional syndrome or progressive dementia, but such a strict classification is inapplicable because none of the cases so far described has conformed entirely to one pattern.

The neurological symptoms in Behçet's syndrome, as with symptoms elsewhere, usually present acutely and recurrent attacks are the rule, the number in each individual ranging from one to as many as seven (Silfverskiöld, 1951). In a few cases, however, notably those with dementia, the onset of the illness has been insidious and its course slowly progressive.

Headache, often intense, has been a presenting symptom in the majority of cases, and with two exceptions (Pallis and Fudge, 1956) has invariably been present at some stage. But headache alone is not conclusive evidence of neurological disease, for it is sometimes due to acute inflammation of the eye (Thomas, 1947). A clinical diagnosis of acute meningitis was made in four cases (Alm and Öberg, 1945; Gray, 1950; Silfverskiöld, 1951; Case 1 of our series) and inflammatory changes in the cerebrospinal fluid were also found in all except 3 of the remainder. The cell count

XUM

has exceeded 100 per c.mm. in only 4 cases and it has been predominantly lymphocytic in all except the 2 with very high total counts. Thus, Alm and Öberg (1945) found 5,400 cells per c.mm. with 84 per cent polymorphs, and Gray (1950) 763 cells per c.mm. with 72 per cent polymorphs. The protein when estimated has been proportionately raised except in one case with arachnoiditis (Pallis and Fudge, 1956) in whom the lumbar cerebrospinal fluid contained 5,400 mg. per 100 ml. Lumbar puncture was not performed on Knapp's case (1941), but in the patient described by Phillips and Scott (1955) and in our Case 3 the cerebrospinal fluid was normal.

Meningitis was uncomplicated on only one occasion, however (Alm and Öberg, 1945), and even in this patient an attack of encephalitis followed within a year. All others during their attacks have had symptoms of involvement of the brain or spinal cord.

There appears to be a particular predeliction for the brain-stem, and this is well illustrated by Gray's case (1950). Three months after the onset of his headache, in addition to lower limb weakness and thermanæsthesia, he developed bilateral external ocular palsies with nystagmus; and shortly before his death five months later was found to have paralysis of conjugate ocular deviation, facial hypæsthesia, left facial weakness and dysphagia. Other examples of brain-stem involvement were recorded by Magni (1951), Phillips and Scott (1955) and Pallis and Fudge (1956), and this was also a feature in 2 of our cases. Case 2 who complained of recurrent diplopia was found to have weakness of upward gaze with spasticity of the jaw, face and tongue and in Case 3 coarse nystagmus, dissociation of ocular movements and loss of upward gaze persisted for about a month.

Signs of Parkinsonism appeared in 3 cases. Magni's patient (1951) relapsed after two years, and during this, his fatal attack, was found to have tremor of the jaw and upper limbs, an expressionless facies and bradykinesia. The outcome was similar in one of the cases described by Pallis and Fudge (1956) and in our Case 2.

In all 3, however, there were features additional to those of Parkinsonism to indicate extensive involvement of the cerebral hemispheres. Thus mental confusion was present in Magni's case (1951) and progressive intellectual impairment with pathological laughter and crying in both the others. Berlin's case (1944) also showed progressive intellectual and emotional disturbance, and is of interest in being the only recorded example of convulsions in Behçet's syndrome.

8 patients including 2 of our own developed spastic weakness of one or more limbs, in 5 of them (Gray, 1950; Silfverskiöld, 1951; Pallis and Fudge, 1956; Case 2 of our series) disturbance of micturition being present in addition. The site of the pyramidal lesion was often obscure, although in a few it was obviously spinal, as in Gray's patient (1950) with a Brown-Séquard syndrome and in the patient of Pallis and Fudge (1956) who had transverse myelitis with arachnoiditis.

XUM

Thus pyramidal signs are common, but disorders of sensation, on the other hand, are not. Anæsthesia of spinal origin was found in 2 cases (Gray, 1950; Pallis and Fudge, 1956) and transient paræsthesiæ were described by Magni (1951), Silfverskiöld (1951) and ourselves (Case 1).

Cerebellar disease and peripheral neuritis have not as yet been observed in Behçet's syndrome but although the meninges and mid-brain, and less often the cerebral cortex and spinal cord, appear to be more susceptible to injury, the diversity of the clinical picture is its most striking feature and no part of the nervous system can be considered immune.

Remissions between attacks are of variable duration and are usually incomplete and the long-term prognosis is poor. Thus of the 13 recorded cases, 3 died within the period of observation (Berlin, 1944; Gray, 1950; Magni, 1951) and 5 were permanently and severely disabled (Silfverskiöld, 1951; Pallis and Fudge, 1956; our Case 2), and although the cases of Knapp (1941) and Alm and Öberg (1945) appeared to have recovered completely they were only observed for a further period of seven years and two years respectively.

Clinical differentiation from tuberculous and other forms of meningitis may be difficult, as in our first case, when there is an excess of cells in the cerebrospinal fluid, but in our experience the glucose content remains within normal limits in Behçet's syndrome. The high cerebrospinal fluid cell count serves to rule out disseminated sclerosis in patients with recurrent weakness and ataxia of limbs, and also the possibility of Alzheimer's, Pick's or Jacob-Creutzfeld's disease in those who present with progressive dementia. In the latter groups of diseases brain-stem signs are furthermore invariably absent.

The oral lesions have occasionally been confused with those of erythema multiforme (Alm and Öberg, 1945), one of the variants of which is the Stevens-Johnson syndrome. This disease when it affects the mucous membranes, however, produces superficial sloughing of the whole mucosa (Church and Sneddon, 1955) and true painful aphthous ulceration is never found. Benign mucous membrane pemphigus, on the other hand, may be difficult to distinguish from Behçet's syndrome.

*Aetiology.*—The ætiology of Behçet's syndrome is in doubt, although many theories have been put forward, among them hormonal imbalance (Moseley, 1941), thrombophlebitis (France *et al.*, 1951), disease of collagen (Phillips and Scott, 1955), virus infection (Behçet, 1938) and allergy (Koch, 1950). Only the last two merit further consideration.

Virus infection is widely assumed, but until recently on slender grounds, to be the cause. In material obtained from the lesions in his original cases Behçet (1938) found very small, reddish-violet extra and intracellular bodies which he considered similar to the elementary bodies of smallpox, and he therefore concluded that the illness was due to a virus. Jensen (1941) was

XUM

unable to confirm his findings, and attempts to grow a virus from the lesions by Curth (1946) and Katzenellenbogen (1946) also failed.

Sezer (1953) took vitreous humour from the enucleated eye of one patient and subretinal serous exudate aspirated from two other patients and injected them into the chorioallantoic membrane of fertile eggs. He claimed thereby to isolate a virus, which he demonstrated by electron microscopy, and which was pathogenic to mice, guinea-pigs and rabbits on intracerebral inoculation. Positive complement-fixation and neutralization tests were furthermore obtained in 12 patients with Behçet's disease using the virus as antigen. Sezer was unable to isolate virus from the anterior chamber of the eye or from the oral and genital aphthæ, and he concluded that the pathogenic agent resided only in the posterior segment of the eye being probably absent from these other sites.

His later experiments (Sezer, 1956) cast doubt on the validity of these observations. Venous blood diluted 1 : 10 in saline, from 20 patients with Behçet's syndrome, was inoculated into the chorioallantoic membrane of 12–13-day-old embryos. Pocks were produced on all the membranes after forty-eight hours' incubation at 36° C. and the number of pocks which appeared during the first week was consistently high, ranging from 30 to 70. These lesions he claimed were specific. Even in the acute viraemia of smallpox such uniformly successful results are unusual, however (Downie *et al.*, 1950; MacCallum *et al.*, 1950), and can be accepted only with reluctance in Behçet's syndrome, a non-virulent, relatively mild disease. Sezer's findings in fact have yet to be confirmed.

Pallis and Fudge (1956) were biased towards virus infection by the natural history of the disease, but this in our opinion is the strongest evidence in favour of allergy. Erythema nodosum is known usually to be an allergic reaction to the tubercle bacillus or the B. hæmolytic streptococcus (Doxiadis, 1951) and most of the other clinical manifestations of Behçet's syndrome, occurring alone, have at one time or other been attributed to allergy.

Little information of ætiological value can be gained from the few autopsy reports so far published. In the fatal case described by Berlin (1944) there were foci of perivascular infiltration in the meninges and brain, with scattered small necrotic lesions in the substantia nigra and one in the floor of the third ventricle. In Magni's case neuronal degeneration with gliosis was present throughout the grey matter, the white matter being apparently normal, and perivascular infiltration was found mostly in the mid-brain where there were also some hæmorrhages. In neither case was demyelination an obvious feature which suggests that these changes were not allergic, for although necrotic and hæmorrhagic lesions alone have been attributed to allergy (Davidoff *et al.*, 1932) demyelination is usually prominent in this type of encephalitis (Cavanagh, 1956). On the evidence available it is probable that both virus infection and allergy

XUM

are concerned in the pathogenesis of Behçet's syndrome, the foci of infection possibly being confined to the eye and the brain, and the more superficial lesions being allergic. The antigen concerned in this hypersensitivity reaction may also be a product of the virus.

## Treatment

The evaluation of any form of treatment in Behçet's syndrome is difficult, owing to its tendency to spontaneous remission and relapse. Not surprisingly, vitamins, œstrogens, antibiotics and antihistaminics have all been tried, but in general with disappointing results; and even local treatment of accessible lesions, such as vulval ulcers, has been ineffective. Phillips and Scott (1955) gave corticotrophin followed by cortisone to 4 of their most severely incapacitated patients, one with involvement of the nervous system, and found the response in all both satisfactory and encouraging. None relapsed on maintenance treatment and they attributed the poor results obtained by previous authors to inadequacy of dosage or duration of treatment.

Pallis and Fudge (1956), on the other hand, gave cortisone in large doses to their patients, 200 mg. reduced to 100 mg. daily for fifteen days and 100 mg. daily for twenty-one days respectively. In both, ulcers continued to appear and it is doubtful if persisting further with treatment would have altered the course of the illness.

We were favourably impressed with the progress of one of our patients (Case 1) given oral cortisone 25 mg. four times daily. Within a few days her headache improved, the eye changes began to resolve, and apart from an occasional small ulcer in the mouth she has remained well on maintenance treatment. In another of our patients, however (Case 3), symptoms of encephalitis appeared while receiving cortisone 50 mg. daily. In spite of this we feel that in acute exacerbations of Behçet's syndrome, especially affecting the eyes or the nervous system, corticotrophin or cortisone should be administered promptly before the changes are irreversible. This view is also upheld by the brief report of Gasner and Feldman (1955). Even when these drugs are effective sequelæ are inevitable if treatment is delayed, and there is probably little indication for their use in the more advanced stages of the disease, as in our second case.

## Summary

3 cases of Behçet's syndrome with involvement of the nervous system are described and analysed together with the 10 cases previously recorded by others.

In Behçet's syndrome there is widespread involvement of nervous tissue, but meningitis, spastic weakness, external ophthalmoplegia with other features of mid-brain disease, and acute confusional states or progressive dementia are its commonest manifestations.

## BEHÇET'S SYNDROME WITH NEUROLOGICAL COMPLICATIONS

*Summaries of Previous Recorded Cases (neurological features only)*

*Interval between onset of illness and first neurological symptom.

*Knapp*, 1941. Female aged 28. *2 years.

Headache, memory impairment, ataxia of arms and Rombergism. Recovery in a month. No recurrence for seven years.

*Berlin*, 1944. Male aged 28. *5 years.

Sudden change in mental state, apathy, depression, frequent headaches and dizzy attacks followed by disorientation and memory defect. Four months later coma after convulsions for three days. *O.E.* Absent supinator and abdominal reflexes, depressed ankle-jerks. *C.S.F.* Cells 95 per c.mm. (55 lymph., 40 poly.). Protein 49 mg. per cent. Died four days later.

*Alm and Öberg*, 1945. Male aged 31. *Since childhood.

1942: Acute meningitis. *C.S.F.* Cells 5,400 per c.mm. (84 per cent poly.). Good recovery.

1943: Acute encephalitis and severe vertical nystagmus.

*C.S.F.* Cells 17 per c.mm. Again recovered completely.

*Gray*, 1950. Male aged 26. *1½ years.

*June* 1947: Headache, nausea, vomiting and right side of body felt cold for four days.

August 1947: Left leg heavy, night sweats, precipitate micturition. *O.E.* Pyramidal signs left leg. Over the next few days right third and fourth cranial nerve palsies developed, then left superior rectus palsy with nystagmus and thermoanæsthesia of lower limbs.

December 1947: Partial right ocular palsy, left eye movements normal, no nystagmus. Brown-Séquard syndrome below L.1 with left pyramidal signs.

February 1948: Fever, occipital headache, vomiting, neck stiffness. *C.S.F.* Cells 763 per c.mm. (72 per cent poly.). Protein 70 mg. per cent. Followed by left facial palsy, paralysis of conjugate ocular deviation to the left, hypoæsthesia of right lower face, dysphagia and death on the third day from respiratory paralysis.

*Magni*, 1951. Male aged 27. *5 years.

Transient paræsthesiæ, paresis and tremor of left arm. Some months later admitted with headache, fever, dysarthria. *O.E.* Impaired upward conjugate gaze, right facial weakness, tremor of tongue and left arm, ataxic gait and bilateral pyramidal signs. *C.S.F.* Cells 40 per c.mm. Protein 60 mg. per cent. Condition static for two years, then sudden onset of fever and mental confusion. *O.E.* Expressionless face, bilateral ptosis, nystagmus, tremor of jaw and upper limbs, bradykinesia. *C.S.F.* Cells 18 per c.mm. Febrile for three months then died in coma.

*Silfverskiöld*, 1951. *Case* 1, male aged 34. *9 years.

August 1947: Fever, severe headache, disorientation, slurred speech, numbness of right arm and leg, alternate laughter and crying. Improved in fourteen days.

September 1947: Similar, more severe, attack. *O.E.* Right hemiparesis and ataxia of right arm. *C.S.F.* Cells 60 per c.mm. (18 per cent poly.). W.R. negative.

October 1947: *C.S.F.* Cells 5 per c.mm. Shortly afterwards weakness of left leg, slurred speech and dysphagia. Severe headache, bilateral ankle clonus but no sensory signs. Weakness gradually improved.

December 1949: Severe paraplegia with paralysis of bladder. *C.S.F.* Cells 40 per c.mm. (mostly poly.). He again slowly improved.

XUM

*Case* 3, female aged 30. *Several years.

April 1947: Sudden fever, neck stiffness, severe headache. *O.E.* Severe paresis of bladder and of right leg with right extensor plantar response. *C.S.F.* Cells 251 per c.mm. (31 per cent poly., 69 per cent lymph.). Culture sterile.

May 1947: Passing urine satisfactorily. *C.S.F.* Cells 11 per c.mm.

Autumn 1947: Slight weakness of both legs.

April 1948: Staggering gait and dragging of right foot. Pain in the arms, weakness and clumsiness of the hands with intention tremor.

June 1948: Paresis of right leg and left arm. Sensibility diminished over right leg and left shoulder. Bilateral ankle clonus and extensor plantar responses. Power in the left arm improved in a few days but she developed neck stiffness and headache. *C.S.F.* Cells 326 per c.mm. (85 per cent poly.) and later paresis of bladder and right leg. Power again improved. *C.S.F.* (July 1948) Cells 2 per c.mm.

October 1948: Neck stiffness, pain and weakness of arms and legs with improvement over a period of two months.

March 1949: "Meningitis." *C.S.F.* Cells 322 per c.mm. (290 poly.).

Autumn 1950: Severe exacerbation, spastic paresis of arms and legs, neck stiffness and disorientation. *C.S.F.* Cells 500 per c.mm.

*Phillips and Scott*, 1955. Female aged 27. *6 months.

Sudden blurring of vision, headache, vomiting, dizziness. *O.E.* Blurred discs, lateral and vertical nystagmus, left lower motor neurone facial palsy, absent abdominal reflexes, doubtful plantar responses, ataxic gait. *C.S.F.* Normal.

Attack transient but followed by minor recurrences.

*Pallis and Fudge*, 1956. *Case* 1, male aged 47. *4 years.

September 1953: Low back pain and difficulty in micturition for three months.

No abnormal neurological signs. *C.S.F.* Protein 510 mg. per cent. W.R. negative.

December 1953: Severe weakness of both lower limbs developing within a few hours, feet "ice cold" with numbness to waist level. Flexor spasms and five weeks later admitted with complete retention of urine. *O.E.* Paraplegia, absent lower abdominal reflexes. Sensory impairment below T.10 dermatome with (?) sacral sparing. *C.S.F.* Lumbar—Few cells. Protein 5,200 mg. per cent. Cisternal—Less than 5 cells. Protein 70 mg. per cent. Cisternal myelography suggested adhesions in the lower thoracic and lumbar regions.

*Case 2*, male aged 44. *15 years.

March 1955: Admitted with stiffness of right arm and slow shuffling gait for 18 months. Mental deterioration with, for a year, outbursts of unwarranted laughter and weeping. *O.E.* Fatuous, expressionless, greasy face, little insight, euphoric and mildly catatonic. Lateral conjugate gaze poorly maintained, and upward conjugate gaze defective, nystagmus. Jaw jerk brisk with clonus. Face spastic, hypertonia of neck flexors, rigidity of right arm and both legs with pyramidal signs but only slight weakness. Marked bradykinesia with stiffness of gait. No sensory or cerebellar signs. *C.S.F.* Cells 6 per c.mm. Protein 90 mg. per cent.

## Acknowledgments

We are grateful to Dr. R. A. Henson, Mr. Arthur Lister and Dr. Kenneth Perry for permission to publish their cases and to Sir Russell Brain, Dr. Henson and Dr. Perry for much helpful advice and criticism.

XUM

## REFERENCES


ADAMANTIADES, B. (1931) *Ann. Oculist., Paris*, **168,** 271.

ALM, L., and ÖBERG, L. (1945) *Nord. med.*, **25,** 603.

BEHÇET, H. (1937) *Der. Wschr.*, **105,** 1152.

—— (1938) *Bull. Soc. franç. Derm. Syph.*, **45,** 420.

—— (1939) *Bull. Soc. franç. Derm. Syph.*, **46,** 674.

—— (1940) *Dermatologica, Basel*, **81,** 73.

BERLIN, C. (1944) *Arch. Derm. Syph., N.Y.*, **49,** 227.

CAVANAGH, J. B. (1956) *Guy's Hosp. Rep.*, **105,** 39.

CHAUFFARD, A., BRODIN, P., and WOLF, M. (1923) *Bull. Soc. méd. Hôp. Paris*, **47,** 841.

CHURCH, R. E., and SNEDDON, I. B. (1955) *Lancet*, **1,** 511.

CURTH, H. O. (1946) *Arch. Derm. Syph., N.Y.*, **54,** 179.

DAVIDOFF, L. M., SEEGAL, B. C., and SEEGAL, D. (1932) *J. exp. Med.*, **55,** 163.

DOWNIE, A. W., MCCARTHY, K., and MACDONALD, A. (1950) *Lancet*, **2,** 513.

DOXIADIS, S. A. (1951) *Medicine, Baltimore*, **30,** 283.

FRANCE, R., BUCHANAN, R. N., WILSON, M. W., and SHELDON, M. B., Jr. (1951) *Medicine*, **30,** 335.

GASNER, W. G., and FELDMAN, P. J. (1955) *N.Y.St. J. Med.*, **55,** 1631.

GRAY, G. S. (1950) *Canad. med. Ass. J.*, **62,** 597.

JENSEN, T. (1941) *Acta derm.-venereol., Stockh.*, **22,** 64.

KATZENELLENBOGEN, I. (1946) *Brit. J. Derm.*, **58,** 161.

KNAPP, P. (1941) *Schweiz. med. Wschr.*, **71,** 1288.

KOCH, H. (1950) *Acta otolaryng., Stockh.*, **38,** 56.

MACCALLUM, F. O., MCPHERSON, C. A., and JOHNSTONE, D. F. (1950) *Lancet*, **2,** 514.

MAGNI, S. (1951) *Riv. oto-neuro-oftalm.*, **26,** 445.

MOSELEY, V. (1941) *J. clin. Endocrin.*, **1,** 346.

PALLIS, C. A., and FUDGE, B. J. (1956) *Arch. Neurol. Psychiat., Chicago*, **75,** 1.

PHILLIPS, D. L., and SCOTT, J. S. (1955) *Lancet*, **1,** 366.

PLANNER, H., and REMENOVSKY, F. (1922) *Arch. Derm. Syph., Wien*, **140,** 162.

SEZER, F. N. (1953) *Amer. J. Ophthal.*, **36,** 301.

—— (1956) *Amer. J. Ophthal.*, **41,** 41.

SILFVERSKIÖLD, B. P. (1951) *Acta psychiat., Kbh.*, **26,** 443.

THOMAS, E. W. P. (1947) *Brit. med. J.*, **1,** 14.

# VIVID DAY-DREAMING
## AN UNUSUAL FORM OF CONFUSION FOLLOWING ANTERIOR CINGULECTOMY

BY

C. W. M. WHITTY AND W. LEWIN

*(From the Departments of Neurology and Neurosurgery, Radcliffe Infirmary, Oxford)*

### INTRODUCTION

SOME degree of confusion is almost invariable for a few days after standard frontal leucotomy, and Freeman (1950) has described the condition in some detail. There is generally correct recognition of persons, but some disorientation for place and time occurs: the latter being often more marked and prolonged. A similar disorientation in time may be seen early after frontal brain wounds, and is reflected in the bizarre manner in which ordinary simple acts, such as eating, washing and dressing, which such patients are quite able to perform, come to occupy hours of time. In both cases, also, there may sometimes be a curious unawareness of the operation or injury, discussed by Stengel (1952), amongst others: and this may persist. Prolonged, possibly permanent, changes may also be found in some aspects of the individual's awareness of himself (Robinson and Freeman, 1954). The operation of anterior cingulectomy, performed in a group of patients with well-preserved intellect and personality, for the treatment of severe obsessional neurosis, afforded an opportunity to study the mental state early after operation. A transient and limited confusional state was fairly consistently found and is thought of sufficient interest to be worth recording. In a setting of general clarity of consciousness, with full orientation for place and person and awareness that operation has been undergone, the patients noted a difficulty, though not a complete inability, in distinguishing between their thoughts and events of the external world. The change is described as an increase in vividness and clarity of thought and dreams, and is illustrated in the case histories given below. The condition was transient, lasting twenty-four hours to three days. At the relevant times, patients were alert, co-operative, and promptly and appropriately responsive to questions and commands. The only evidence of a more widespread confusion was a very limited disorientation in time; a tendency to misplace events in the sequence of time since operation. There was also a tendency for speech to be rather more disinhibited than formerly, both in content and format.

XUM

## Clinical Material

Details of the extent and method of operation in anterior cingulectomy have been given elsewhere (Whitty *et al.*, 1952). It consists essentially of a limited bilateral cortical ablation in Brodmann's Area 24, extending back from the anterior end of the genu of the corpus callosum for 3–4 cm., is 1 cm. wide and 1 cm. (full thickness of cortex) deep. Autopsy results confirm that the small extirpations planned were in fact achieved, and there was no evidence of more extensive unintentional damage (Whitty, 1955). Since this unusual type of confusion was first noted, it has been looked for in 10 patients and found in 8. Of the 2 in which it did not occur, one had a very incomplete ablation owing to operative difficulties, and one had the usual removal, but differed from the others in having clinical and EEG evidence of "temporal lobe" epilepsy.

The following 3 cases illustrate the changes observed.

*Case 1* (R. I. 142371).—A business man aged 58 had had a severe tension state with obsessional and depressive features for over five years. Cingulectomy was performed in 1951. Relief of symptoms was considerable for three years, but he then relapsed with depression, and had an orbital leucotomy a year later.

Forty-eight hours after cingulectomy he was fully orientated for place and person, though uncertain whether it was one or two days since operation. In response to questions as to what he had been doing that day, he replied: "I have been having tea with my wife." Without further comment from the questioner, he continued: "Oh, I haven't really. She's not been here today. But as soon as I close my eyes the scene occurs so vividly, I can see the cups and saucers and hear her pouring out, then just as I am lifting the cup for a drink I wake up, and there's no one there."

*Q.* Do you sleep a lot, then?
*A.* No, I am not asleep—it's a sort of waking dream . . . even with my eyes open sometimes.
*Q.* How did you sleep last night?
*A.* I didn't sleep much. I was on the go all the time: friends coming in to talk to me.
*Q.* Did Sister let them in?
*A.* No, they weren't really there, of course, but that's what I mean (referring to earlier questions about his thinking). My thoughts seem to be out of control, they go off on their own—so vivid. I am not sure half the time if I just thought it or it really happened.

A feature that emerged in response to questions was that the dreamed or thought experience was often recurrent or repetitive. Happenings in the external world would interrupt it for a time, and then it would appear to be resumed where it had been left off.

The effect became less vivid in the next twenty-four hours and by four days post-operatively it had cleared, though he could still recall it with surprise.

*Case 2* (R. I. 170075).—A schoolmistress aged 31 had suffered for nine years with a severe obsessional neurosis, completely disabling her for two years before cingulectomy in 1954. A year later she was leading a normal wage-earning life, though some symptoms were still present.

Twenty-six hours after operation she was orientated for place and person, though inaccurate in assessing the sequence of post-operative events. Her speech and manner

were slightly uninhibited. General tension was strikingly lessened, though she still expressed concern about her main phobia of swallowing pins.

She said: "The nurses drop pins everywhere, in my bed and clothes."

*Q.* Do they really?
*A.* Well, I think they do.
*Q.* Have you seen them doing it?
*A.* No exactly; but when I doze off I see it.
*Q.* You mean you dream it?
*A.* It's more thinking than dreaming; but that's the trouble, my thoughts seem so vivid I can't remember what I think and what happens.
*Q.* How did you sleep last night?
*A.* All right, I suppose; but there was a lot of noise and two people talking about me just outside the door.
*Q.* What were they talking about?
*A.* About my symptoms. It was two of the doctors.
*Q.* Were they really there?
*A.* I seemed to hear them whenever I dropped asleep, but they may have been part of my dreams. I was dreaming all night, and I felt it was all really happening.
*Q.* But you could tell if you really heard them.
*A.* Yes, I can work it out. But ever since I left the theatre I just can't distinguish between phantasy and reality.

This cleared gradually in the next forty-eight hours. A week later she could recall and describe the difficulties she had had, but six months after the operation the memory was less clear.

*Case 3* (R. I. 156661).—A butcher aged 60 had had a severe obsessive ruminative neurosis with depressive features for at least four years. Cingulectomy was performed in 1952, and when last seen three and a half years later he was free from symptoms and having no psychiatric treatment.

About forty hours after operation he was alert and fully orientated for place and person. He was inaccurate in assessing the time since his operation, and in placing happenings during the interval, but this disorientation was slight and had to be sought for. In response to questions he spoke of having spent the night in a field near his home; but he amended this to say he had dreamt he had. He gave a vivid description of the "dreams" in which he was standing by an advertisement hoarding in a field near his home—a place he used to seek when his symptoms were especially troubling him. The dream was unusual, both because he did not usually dream, and because it recurred in the same form whenever he dozed off and had a subjective continuity about it. In the morning he thought at first that he had really been to this spot.

During the first post-operative day he also thought one of his brothers and his wife had visited him, and could recall their appearance and conversation. In fact, he had had no visitors. Here, also, he was aware that he had imagined this occurrence, and was chiefly impressed with the vividness of the experience, which he emphasized continually in conversation. At first, he had to be drawn out to speak of it, and reassured that it was a transient effect, as he was rather ashamed about it.

Four days after operation he no longer noticed this phenomenon, and he had ceased to dream, or at any rate to recall his dreams, at night—a condition which was normal for him.

The essential change in these cases seems to be an increase in vividness of thoughts and dreams, rather than any decrease in that of external reality. Thoughts are not only vivid, but they seem to pursue their own course and

to have something of the autonomy of external events. Dreams may have an unusual repetitive or continuous quality, so that if they are interrupted on waking the same dream appears to recur on sleeping again. Patients spontaneously use such phrases as, "I can't distinguish between dreams and reality." The condition is reminiscent of a depersonalization syndrome in reverse. Confusion is probably not the right word for it, since patients are fully orientated and both clearly aware of the phenomenon and able to describe and discuss it. In some cases it may emerge spontaneously in conversation as in Case 1. In others it has to be sought for, as the patient is worried about it and tries to conceal it.

## Discussion

These changes have not been seen following frontal leucotomy. They may, of course, occur, but be submerged in the more widespread disorientation that is present. If so, this only emphasizes the interest of their occurrence, in a more clear-cut form, following the functionally much more limited operation of cingulectomy.

In the normal individual the wish is occasionally father to the thought, and intentions may be misremembered as accomplished facts; but this differs from what we are considering, because in the former for a time self-deception is complete. In delirium, also, there is an inability to distinguish thought from reality, but this, too, is not comparable, for here there is profound general confusion, and external reality is ignored or misrepresented. Many normal children under 5 years of age have great difficulty in distinguishing between phantasy and reality. A vividly told story or some wished-for event may be recalled and recounted as a real happening. The inability to distinguish is usually not complete, and they may in retrospect recall the phantasy and its vividness and know that it was not real. This is much more like the condition we are discussing. Unfortunately, nothing is known of which particular cerebral circuits require activating or maturing before this phase of childhood passes.

Focal hallucinations are perhaps also related, for here, too, there may be no confusion, and the unreality of the phenomenon may be half appreciated.

Parfitt (1956) in analysing early symptoms of schizophrenia, has quoted phrases which closely mimic those used by our patients. "I get confused between false and true memories." "I cannot remember whether things that have happened have really happened or not." Here however the change was usually in a setting of other mental symptoms and was progressive: though in the early case, mentally accessible and cooperative, it sounded strikingly similar.

The comparative brevity of the phenomenon suggests that it may be the effect of a discharging lesion, rather than an interruption of fixed anatomical pathways. Certainly, electrocorticograms of adjacent frontal areas,

XUM

and EEGs immediately after operation, show much abnormal high voltage activity not previously present. If the clinical change noted is the result of injury potentials discharged at the edges of the excision, it would be interesting to know to what parts of the cortex the discharge passes. Anatomical links exist, though probably transsynaptic, between cingulate cortex and that of the medial temporal lobe. Moreover, in monkeys the profound behaviour changes following cingulectomy are strikingly similar to those seen after temporal lobectomy. In the clinical sphere, depersonalization, derealization, altered states of awareness of the external world, and even vivid increased dreaming, are all seen occasionally as symptoms of temporal lobe lesions. They may provide a clue to the condition here described and exhibit it as in part a transient temporal lobe dysfunction. Whatever its neurological substrate, there is no doubt that a cerebral mechanism fundamental to normal mental life has been temporarily disturbed.

## Summary

A transient limited confusional state is described as occurring in 8 out of 10 patients after cingulectomy.

The condition consists essentially of an increased vividness of thoughts, dreams and phantasies, so that there is difficulty in distinguishing between mental events and happenings in the external world.

The possible neurological mechanisms involved are briefly discussed.

## REFERENCES

FREEMAN, W., and WATTS, J. W. (1950) "Psychosurgery," 2nd ed. Springfield, Ill.
PARFITT, D. N. (1956) *J. ment. Sci.* **109,** 671.
ROBINSON, M. F., and FREEMAN, W. (1954) "Psychosurgery and the Self." New York.
STENGEL, E. (1952) *J. ment. Sci.*, **98,** 382.
WHITTY, C. W. M. (1955) *Proc. R. Soc. Med.*, **48,** 463.
——, DUFFIELD, J. E., TOW, P. M., and CAIRNS, H. (1952) *Lancet*, **1,** 475.

# THE EFFECTS OF SOME DRUGS ON THE ELECTRICAL ACTIVITY OF THE BRAIN

BY

P. B. BRADLEY AND J. ELKES

*Department of Experimental Psychiatry, Medical School, Hospitals Centre, Birmingham 15*

## INTRODUCTION

There is no lack of data on the effect of drugs on the electrical activity of the brain. Ever since Berger (1933) observed the effects of barbiturates on the human alpha rhythm numerous studies have attempted to describe and interpret the effects of drugs on the electrical activity of cortical and subcortical areas (Adrian and Matthews, 1934; Gibbs, Gibbs and Lennox, 1937; Grinker and Serota, 1938 and Gerard and Libet, 1940). The effect on the activity of isolated units has also been studied (Amassian, 1952). In so far as they concern the so-called autonomic drugs, which form the burden of this paper, particular attention has centred on the possible role of acetylcholine as a central neurohumoral transmitter. Sympathomimetic and other non-cholinergic agents have received relatively little attention, though, with the recent advent of drugs exerting peculiar effects on mental function, some shift of interest is now apparent. The field has been reviewed by Toman and Davis (1949).

The drugs in question have been applied by various routes. Thus Bonnet and Bremer (1937) and Bremer and Chatonnet (1949) injected acetylcholine and physostigmine into the carotid artery in unanæsthetized preparations (*encéphale isolé*). They found that acetylcholine, in quantities of less than 0·5 $\mu$g. caused a reduction in voltage and rise in frequency of the electrocortical activity. Physostigmine and neostigmine given intra-arterially in doses of 0·1–0·5 mg./kg. produced similar effects to those of acetylcholine, but these were longer lasting. All these effects could be abolished (or blocked) by intravenous atropine in doses of 0·5 mg./kg. Hampson *et al.* (1950) administered di-isopropyl-fluorophosphate (DFP) in graded doses by the intracarotid route. They observed the emergence of seizure patterns characterized by high amplitude waves which could be related to a decrease in the cholinesterase activity of cortical tissue.

Topical application to the exposed cerebral cortex of anæsthetized



XUM

animals has provided another route, the electrical activity being recorded either from the area to which the drug had been applied, or adjacent areas. Miller, Stavraky and Woonton (1940), obtained spike discharges, and also motor effects, when they applied a 1 per cent solution of acetylcholine to an area of exposed cortex previously treated with 1 per cent physostigmine. They also found that atropinization blocked these effects. Chatfield and Dempsey (1942) obtained similar effects with 1 per cent acetylcholine following 1 per cent neostigmine, and found that alone, acetylcholine exerted no effect. They also noted that atropine (1 mg./kg., intravenously) did not abolish the spike discharge. Brenner and Merritt (1942) obtained localized discharges with acetylcholine alone, but used higher concentrations (2·5 to 10 per cent). They observed that neostigmine enhanced the responses and lowered the threshold to acetylcholine. Intravenous atropine (1 mg./kg.) did not antagonize these effects.

Forster (1945) injected acetylcholine intracisternally in cats in doses of 10 to 25 mg. and obtained depression of electrical activity, followed by high voltage discharges. Similar effects were obtained by Forster and McCarter (1945) with 5 to 25 per cent solutions of acetylcholine applied to the exposed cortex, and Forster, Borkowski and McCarter (1946) found that the depression of activity preceding the spike discharge was not related to the systemic effects, and could be obtained with solutions of acetylcholine which were too weak to produce a discharge. This initial depression of activity was also observed by Beckett and Gellhorn (1948) and Hyde, Beckett and Gellhorn (1949) who were able to show that high voltage discharges from the cortex could be obtained with a variety of agents having little in common. These included mescaline, streptomycin and acid fuchsin, as well as established convulsants such as metrazol and picrotoxin. More recently, depression of electrical activity on local application of acetylcholine (in 2 to 20 per cent solutions) was observed by Essig, Adkins and Barnard (1953). This was occasionally followed by paroxysmal spikes. Cooke and Sherwood (1954) obtained an increase in spindle activity in *encéphale isolé* preparations after intraventricular injections of 10 to 20 $\mu$g. of acetylcholine. This was depressed by atropine.

Similar patterns of activity to those seen with intra-cisternal or topical application of the drugs in question have been obtained by way of the intravenous route. Thus DFP, when administered in doses of 1 to 2 mg./kg. produced *grand mal* patterns (Freedman *et al.*, 1949) and this effect could be abolished by intravenous atropine in doses of 2 to 4 mg./kg. Funderburk and Case (1951) found that atropine, when administered alone in doses of 0·4 to 1·2 mg./kg. intravenously, produced sleep patterns in the EEG of curarized cats. They also noted that whereas atropine increased the spiking due to the topical application

of curare and penicillin, it decreased or abolished that due to acetylcholine. Wikler (1952) recorded the electrical activity of the brain in unanæsthetized dogs, and observed that although the administration of atropine was followed by excitement, the EEG showed "sleep patterns." A similar dissociation between behaviour and electrical activity using atropine, was observed independently by Bradley and Elkes (1953*b*) in the conscious cat.

All workers draw attention to the similarity between the high voltage discharges obtained with acetylcholine and epileptic seizure records, and there have been numerous suggestions (Tower and Elliott, 1952) that acetylcholine may play an important part in the mechanism of epileptic seizures. On the other hand, it is well known that high voltage discharges can be obtained by applying a variety of agents to the cortex (Hyde, Beckett and Gellhorn, 1949; Funderburk and Case, 1951).

Relatively little attention has been paid to the effects of sympathomimetic agents on the electrical activity of the brain. Toman and Davis (1949) found no change in the EEG of animals treated with amphetamine. Changes in the EEG have been observed in the conscious cat following the administration of *r*-, *d*- and *l*-amphetamine (Bradley and Elkes, 1953*a*) and in the dog following *d*-amphetamine (Schallek and Walz, 1953). In all these experiments the changes in the EEG paralleled the effects on behaviour. The effects of adrenaline on the EEG and its possible significance in the mechanism of arousal, has recently been studied by Bonvallet, Dell and Hiebel (1954), who recorded the effects of this drug in acute preparations sectioned at various levels of the brain stem. The effect of *d*-lysergic acid diethylamide (LSD 25) on the electrocorticogram in rabbits has been studied by Delay *et al.* (1952) and in the conscious cat by Bradley and Elkes (1953*b*).

Many of the reports on the effects of drugs on the electrical activity of the brain are contradictory. They are, in the main, based on experiments carried out in anæsthetized preparations, or in acute preparations immobilized by spinal section, or by curare. Behaviour could not readily be studied in these experiments. Since, however, some drugs do affect behaviour, and the relation between electrical activity and behaviour seemed particularly important, some time was devoted to the development of a technique for the recording of electrical activity simultaneously with behaviour in the conscious, unrestrained and unanæsthetized animal (Bradley and Elkes, 1953*c*). An additional advantage of this technique was that it enabled the operator to become familiar with the normal behaviour and EEG patterns of each animal. Slight effects produced by drugs could thus be more easily detected, and the differences between individual animals be given their due weight.

In addition to the chronic unrestrained preparations, acute preparations were also used. These were the so-called *encéphale* and *cerveau*

*isolé*, (Bremer, 1935, 1936), where both systemic blood pressure and heart rate could be recorded simultaneously with the electrical activity. In addition, drugs could be injected both by the intracarotid and intravenous route, and the effects of the planes of section on the responses observed.

The aim of the study was an attempt to answer the following questions:

(*a*) What is the effect of the drugs studied on the electrical activity of the brain and on behaviour in the normal conscious animal?

(*b*) Is there any correlation or lack of correlation between electrical activity and behaviour with any of these drugs?

(*c*) Is there any interaction between the drugs used?

(*d*) Can any clues as to their mode of action be derived from these experiments?

The preliminary results of the experiments which follow have been communicated to the Physiological Society (Bradley and Elkes, 1953*a* and *b*, and the 3rd International EEG Congress (Bradley, 1953).

## Methods

Fifty-four cats and six monkeys were used in this study. Most of the experiments were carried out in the conscious animal using chronic cat preparations with implanted electrodes. The operative technique has already been described (Bradley and Elkes, 1953*c*). In a few cases a cannula for the intraventricular injection of drugs (Feldberg and Sherwood, 1953) as well as electrodes were implanted. In all, fourteen chronic preparations were used, and experiments were carried out over a period of approximately six months before killing the animals and checking the electrode placement. For the simultaneous observation of behaviour, a specially constructed chamber (Bradley and Elkes, 1953*c*) was used. An occasional film record was also made.

For acute experiments, the Bremer preparations (the so-called *encéphale isolé* and *cerveau isolé*) were used almost exclusively. These were prepared under ether anæsthesia combined with local infiltration of procaine. A tracheal cannula was introduced, and, wherever necessary, the carotid or femoral artery and the femoral vein were cannulated.

To prepare the *encéphale isolé*, the neck muscles were dissected away from the occipital region of the skull, the occipital joint exposed and the dura incised between the foramen magnum and the first cervical vertebra. The spinal cord was then transected through this aperture by means of a blunt leucotome, whilst full anæsthesia was maintained. Artificial respiration was then applied. Cortical recording electrodes were inserted through burr holes in the skull to record from various regions of the cortex, and an earthing electrode inserted into the bone overlying the frontal sinus. The electrodes were of the same type as those used in the chronic preparations. When all operative procedures had been completed, the administration of ether was discontinued and artificial respiration alone maintained. At least one hour was allowed to elapse before the experiment was commenced. This ensured an adequate wearing off of the anæsthetic. At the end of each experiment the brain was dissected out and fixed in formol saline to confirm the electrode positions, and to check the completeness of the spinal section.

In some early experiments the *cerveau isolé* was prepared from the *encéphale isolé*;

XUM

in others the mid-brain section was made in the intact animal. This was done in two ways. In some cases, a leucotome was inserted on either side of the mid-line through holes just anterior to the supra-occipital ridge, and slid down over the edge of the tentorium until it reached the base of the skull. In more recent experiments, a new method of making the lesion was tried, and found to be more successful. Here a fronto-parietal bone flap was turned, exposing almost the whole of one cerebral hemisphere. The dura was then incised and the occipital lobe gently pulled forward to give a clear view of the superior colliculus. The lesion was then made at the inter-collicular level, using suction. A fine glass pipette was employed and the negative pressure kept to a minimum. The tissue was removed very gently, and the lesion gradually extended to the opposite side to give a complete transection of the mid-brain. Local bleeding or œdema was controlled by means of small pledgets of gelatine sponge. The occipital lobe was then allowed to fall back into place, the bone flap replaced and held in position by one or two sutures in the temporalis muscle. Recordings of electrical activity were taken from the opposite, undisturbed hemisphere. In all cases the brain was fixed in formol saline at the end of the experiment, and the position and extent of the lesion checked subsequently.

Five experiments were carried out under barbitone anæsthesia where the effects of barbiturates in combination with other drugs were being studied.

Recordings of blood pressure in the acute experiments, from either the carotid or femoral arteries were made either on a kymograph, or using an electronic manometer which recorded the blood pressure on the same trace as the electrical activity.

In all experiments recordings of electrical activity were made with bipolar electrode connections. A Mitchell 6-channel Electroencephalograph, in conjunction with an Ediswan Low Frequency Wave Analyser was used in early experiments. Later, 4-channel Ediswan Portable Recording Equipment was used.

TABLE I

| *Drugs* | *Preparations* |
|---|---|
| Physostigmine sulphate<br>Physostigmine salicylate<br>Neostigmine methylsulphate<br>Di-*iso*propylfluorophosphate<br>Atropine sulphate<br>*d*-hyoscyamine sulphate<br>*l*-hyoscyamine sulphate<br>*r*-amphetamine sulphate<br>*d*-amphetamine sulphate<br>*l*-amphetamine sulphate<br>Mescaline sulphate<br>*d*-lysergic acid diethylamide. | Conscious animal<br>*Encéphale isolé*<br>*Cerveau isolé*<br>Anæsthetized animal |

A list of drugs, together with the types of preparation, is given in Table I. In most cases, the solutions were freshly made up in normal saline, or sterile distilled water. In a few cases dispensed solutions were used. In experiments in the conscious animal, drugs were given mostly by the intraperitoneal route, but in some experiments they were given orally, intramuscularly or subcutaneously, and in others by intraventricular injection. In acute experiments, drugs were administered either by way of a cannula in the femoral vein, or by intracarotid injection.

XUM

## Results

### I. The Electrical Activity of the Brain of the Normal Conscious Cat

The spontaneous resting activity of the unrestrained conscious cat has been described by a number of authors (Rheinberger and Jasper, 1937; Bradley, 1952; Hess, Koella and Akert, 1953) and their findings are in very close agreement. Our own observations may be summarized as follows:

(*a*) In the waking, fully alert state, with the animal showing maximum awareness of the environment and spontaneous movement, the amplitude of the electrical activity was at a minimum. No dominant rhythm could be detected and components were present at many frequencies. These usually ranged between 15 to 20 c/s and 25 to 30 c/s (Hess *et al.* have observed frequencies up to 40 c/s). The appearance of the record was flat and desynchronized (fig. 1A). This type of record characterized

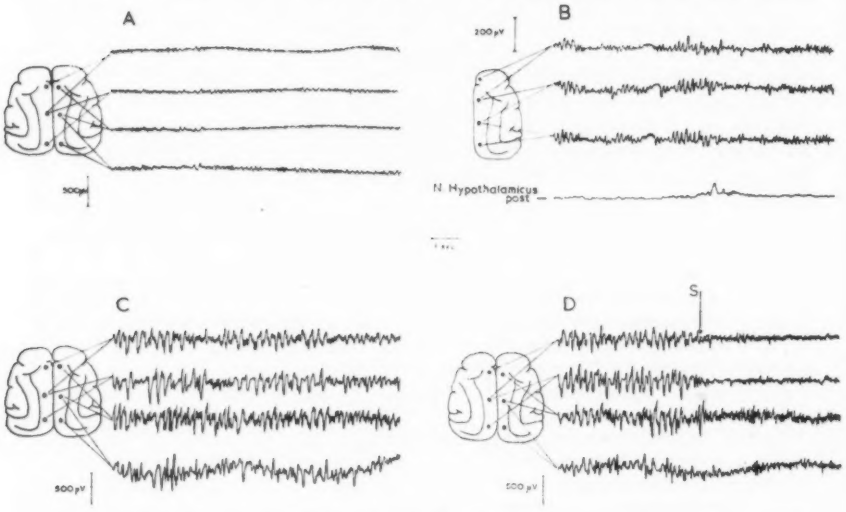


Fig. 1.—Typical records of the electrical activity of a normal conscious cat in different behavioural states. A, fully alert; B, quiet; C, drowsy; D, arousal from the drowsy state through a sensory stimulus (noise) at "S."

the alert state in all our animals, and appeared in all regions from which recordings were taken. It was referred to as the "alert" or "activation" pattern.

(*b*) In the resting or relaxed state, in which the animal was often seen sitting or lying down, with its eyes open or closed and obviously not markedly interested in its environment, bursts of rhythmic activity

at a frequency of 5 to 8 c/s were noted (fig. 1B). These had an amplitude of up to 200 $\mu$V. but were not uniformly distributed over the whole of the cortex. They appeared more in the cortical areas which were not primary sensory or motor areas and in the medial nuclei of the thalamus rather than the lateral nuclei. In some animals these bursts were often preceded and followed by shorter bursts at frequencies between 12 and 16 c/s.

(*c*) The third stage corresponded to drowsiness or light sleep. In this state the electrical activity consisted of slow waves at 1 to 3 c/s with an amplitude of up to 500 $\mu$V., together with bursts of spindle activity at 12 to 15 c/s (fig. 1C). This activity appeared in all the regions from which recordings were taken.

In either the resting or drowsy state an arousal response could be obtained if a suitable sensory stimulus was applied. This could be either tactile or auditory, the latter usually being more convenient, and, irrespective of the previous state of the animal, the activation pattern was immediately produced, the behaviour changing correspondingly (fig. 1D). In no case did we fail to obtain this response in the normal animal; it was regularly tested for in every experiment before any of the drugs were administered.

Although the patterns described above were those seen normally in most of the chronic preparations, and no other type of pattern was encountered, there were individual variations in certain cases. These however, always followed the observed behaviour. For example, in one animal which was very restless and never really settled down in the constant environment chamber (although it was put in at weekly intervals over a period of months), the activity characteristic of the drowsy state never fully developed. Equally, the animal was never seen to be drowsy or sleeping under experimental conditions. On the other hand some animals settled down very quickly, and after two or three periods of acclimatization would go to sleep almost at once. Here only a transient response to the arousal stimulus was usually seen. This was characterized behaviourally by merely lifting the head and opening the eyes.

There were also variations between experiments with the same animal on different occasions. Some animals were more restless on some occasions than others but always showed the type of electrical pattern that one would expect from the observed behaviour. We never noticed any change in the behaviour of these animals as a result of previous experiments. They remained perfectly friendly and even affectionate, and never resisted being manually restrained for injections.

These observations serve to emphasize the importance of observing behaviour simultaneously with electrical activity; of observing each animal over long periods so that the operator could become thoroughly

XUM

familiar with the normal individual pattern of each animal; and of providing a relatively constant environment so that, as far as possible, the only variable operating during the experiment was the pharmacological agent under study.

## II. The Effects of Parasympathomimetic and Parasympatholytic Substances on Electrical Activity, and on Behaviour

### (*a*) *In the Conscious Animal*

(i) *Physostigmine.*—This drug was given alone or preceding other drugs in twelve experiments in the conscious chronic preparation and produced consistent changes in the electrical activity of the brain. Within five to ten minutes after the administration of the drug, the electrical activity from all regions consisted of flat low amplitude potentials similar to those seen in the normal alert animal (fig. 2B). However, the behaviour of the animals was unchanged and they remained quiet, or even apparently sleeping, whilst the electrical activity was of a type seen in the normal animal only in the waking state. The dose required to produce these effects varied between 0·2 to 1·0 mg./kg. for the salicylate, which was used in five of these experiments and between 0·05 and 0·1 mg./kg. for the sulphate, the drug in all cases being given intraperitoneally. No peripheral effects were obtained with these doses, but with larger doses salivation, incontinence and respiratory embarrassment were observed and the animals became more alert in their behaviour as a result of these effects. Smaller doses than those given above produced a less marked change in electrical activity.

Recovery of the normal electrical pattern was usually complete in two or three hours but the effects could be abolished earlier by the administration of atropine (fig. 2C) or *l*-hyoscyamine.

There was no noticeable change in the response to rhythmic photic stimulation after these doses of physostigmine.

(ii) *Neostigmine.*—This was given in two experiments, in the form of the methyl sulphate, in doses of 0·2 and 0·4 mg./kg., intraperitoneally. With the smaller dose, no change in the electrical activity was observed and with the larger dose marked peripheral effects were seen. These included excessive salivation, incontinence, muscular fasciculation and respiratory embarrassment; the effects on the electrical activity were those which would be expected from such a disturbance of behaviour. Thus when the animal was quiet, the electrical activity was unchanged.

(iii) *Di-isopropylfluorophosphate* (DFP).—This drug has been used in only two experiments in the conscious animal owing to its long-lasting effects. In each case the experiment was pre-terminal and the animals were pre-medicated with atropine (1·0 mg./kg.). The respective doses of DFP were 3·0 and 6·5 mg./kg. in the two experiments. With the

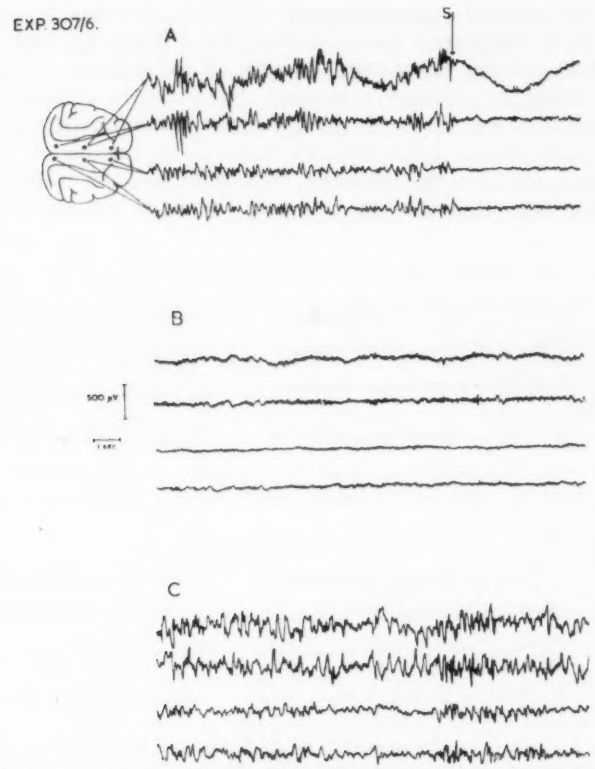


FIG. 2.—Records from an experiment on a chronic preparation in which physostigmine was given first, followed by atropine. A, control record of the conscious animal showing an arousal response; B, ten minutes after an intraperitoneal injection of 0·08 mg./kg. of physostigmine sulphate; C, twenty minutes after the subsequent injection of 3·0 mg./kg. of atropine sulphate (intraperitoneally).

smaller dose, (3·0 mg./kg.) no change in the electrical activity was seen. The larger dose (6·5 mg./kg.) caused an increase in the amount of fast activity in the record, and bursts of activity at 20 to 30 c/s (with an amplitude of about 100 $\mu$V.) were observed. The behaviour changes were very slight. The rate of respiration increased slightly (from 35 to 46 per minute with 3·0 mg./kg.) and some unsteadiness of gait was noted. Both animals were less active and did not move unless they were disturbed. No change in the response to rhythmic photic stimulation was observed.

(iv) *Atropine.*—This drug was given alone, or preceding other drugs in twenty-two experiments in the conscious animal. In eighteen of

these it was given by intraperitoneal injection, in doses of 1·0 to 3·0 mg./kg. of the sulphate. Doses of less than 1·0 mg./kg. had no effect on electrical activity but caused dilation of the pupils. Larger doses (2·0 to 3·0 mg./kg.) caused a marked change in the electrical activity in all cases. Some 15 to 20 minutes after the administration of the drug large amplitude slow waves appeared in all regions of the cortex and in the leads from the thalamus, hypothalamus and caudate nucleus (fig. 2C and 3B). This activity was very similar to the activity seen in

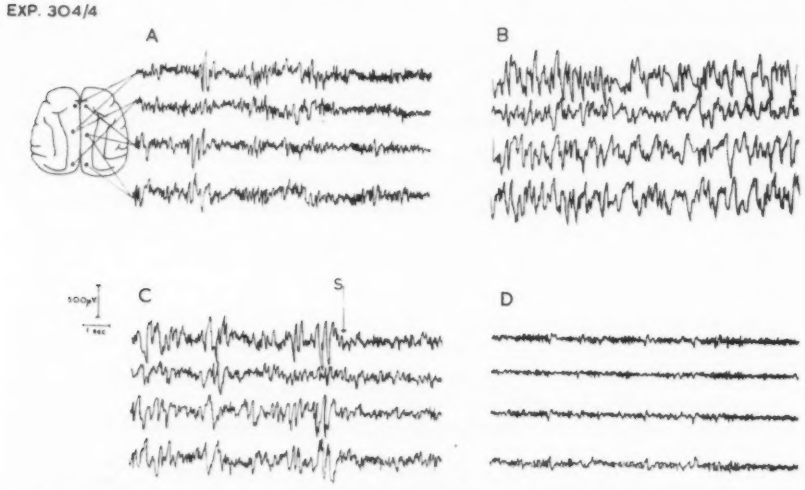


FIG. 3.—Records from an experiment in which atropine was given to the conscious animal and followed by physostigmine in divided doses. A, control record; B, twenty minutes after an intraperitoneal injection of 2·0 mg./kg. of atropine sulphate; C, ten minutes after the subsequent injection of 0·5 mg./kg. of physostigmine sulphate (intraperitoneally), showing the return of the arousal response; D, fifteen minutes after a total of 0·9 mg./kg. of physostigmine had been given.

the drowsy or sleeping state, but the amplitude was sometimes larger. There were also bursts of spindle activity at 12 to 15 c/s in most cases, similar to those seen in the drowsy animal. In all these experiments, although large amplitude slow waves dominated the electrical recordings, sleep or drowsiness were never observed and the animals remained fully awake. In some cases slight excitement was noted after the drug had been given. The application of an arousal stimulus (e.g. a noise) which would normally alert the animal and produce a corresponding change in electrical activity, evoked the normal behaviour response (i.e. alerting) but produced no change in the electrical patterns. Thus the slow waves persisted irrespective of the behaviour of the animal.

When doses of between 1·0 and 1·5 mg./kg. were used the slow activity appeared in bursts and was less persistent. With these lower doses it could still be blocked by sensory stimuli. No change was observed in the response to rhythmic photic stimulation after atropine sulphate, and the response recorded from the visual cortex was often seen superimposed on the slow activity. This effect was never observed when the slow activity of the drowsy state was present in the normal animal. Under such conditions the response to photic stimulation was very much reduced or lost.

In four experiments atropine sulphate was injected into the lateral ventricle in the conscious animal by means of an implanted cannula. The doses used were between 200 and 500 $\mu$g., and the behavioural effects observed were similar to those described by Feldberg and Sherwood (1954). These consisted of increased liveliness and restlessness, together with licking, defæcation and vomiting in the early stages, and with the largest doses. There was also an increase in the respiratory rate. In all four experiments the electrical activity was of the alert type associated with the increased liveliness of the animals (fig. 4B). In none of these

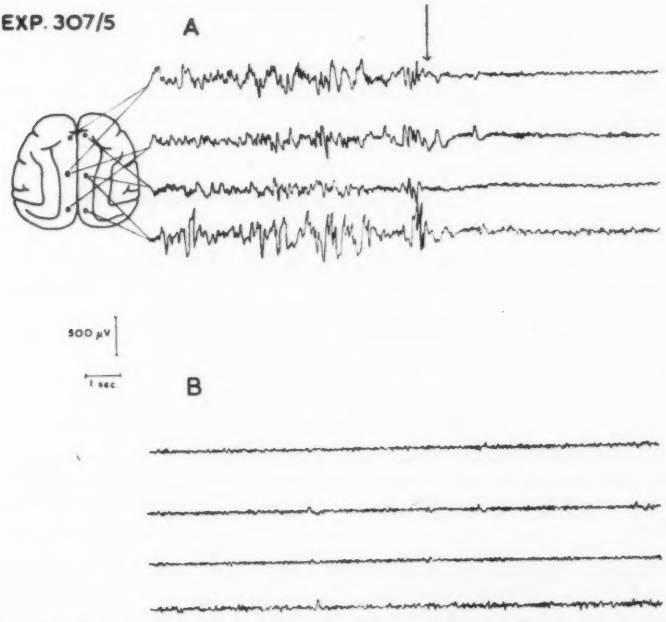


FIG. 4.—A, Control record of normal conscious cat showing an arousal response. B, seventeen minutes after the injection of 300 $\mu$g. of atropine sulphate into the lateral ventricle of the brain.

experiments was any slow activity, similar to that seen when the drug was injected intraperitoneally, observed.

(v) *d-Hyoscyamine sulphate*.—This drug was given in two experiments in doses of 5·0 and 10·0 mg./kg., by intraperitoneal injection. In neither case did it have any effect on behaviour or electrical activity (fig. 5B).

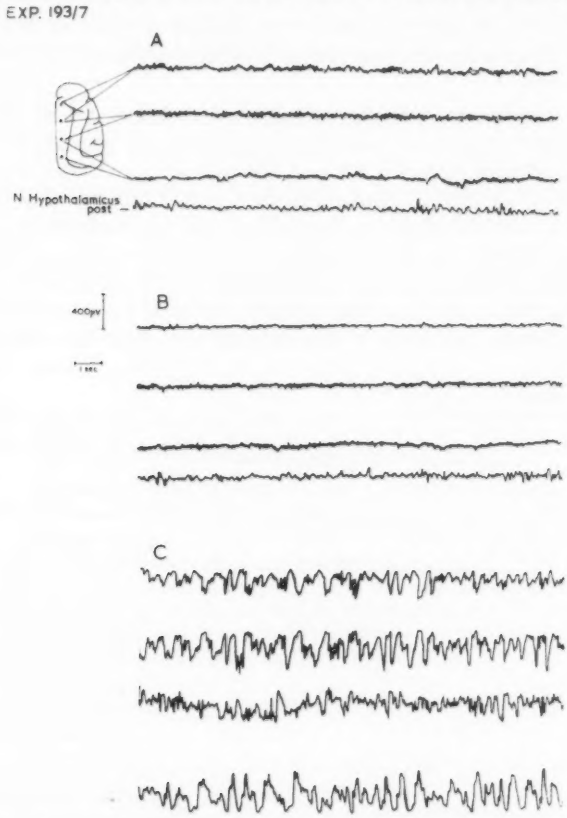


FIG. 5.—A, Control record of normal conscious cat in the alert state. B, twenty minutes after the injection of 10 mg./kg. of *d*-hyoscyamine sulphate intraperitoneally; C, ten minutes after the injection of 1·0 mg./kg. of *l*-hyoscyamine sulphate intraperitoneally.

(vi) *l-Hyoscyamine sulphate*.—This was used in four experiments in doses of 1·0 to 4·0 mg./kg., given intraperitoneally. It produced very similar changes in electrical activity to those observed with atropine sulphate (fig. 5C). There was never any change in behaviour, and in no case was any excitement seen.

(vii) *Combinations of atropine or l-hyoscyamine and physostigmine.*—In three experiments atropine sulphate (2·0 mg./kg.) was given first, and followed by physostigmine (0·7 to 2·0 mg./kg.). In another three experiments *l*-hyoscyamine (1·0 to 2·0 mg./kg.) was given first and this was also followed by physostigmine in similar doses. In all of these experiments the slow activity was abolished after the physostigmine had been given, and the record was similar to that seen when the drug was used alone, although somewhat larger doses were required (fig. 3D). No peripheral effects were observed.

In one of these experiments physostigmine was given in divided doses and it was found that the effect of a small dose was not to abolish the slow activity altogether, but to make it less persistent and also more responsive to sensory stimuli. The arousal stimulus, however, would produce only a brief alerting of the electrical activity, and the slow waves very soon reappeared (fig. 3C). A further injection of physostigmine abolished the slow activity altogether (fig. 3D).

In one experiment physostigmine was given first in a normal dose (0·08 mg./kg.) and then followed by atropine sulphate. It was found that the slow activity could still be obtained, but that a larger dose of atropine (3·0 mg./kg.) was required (fig. 2C). In another experiment a similar result was obtained when physostigmine was followed by *l*-hyoscyamine.

(viii) *Combinations of atropine, l-hyoscyamine and neostigmine.*—In one experiment neostigmine was given after atropine (3·0 mg./kg.), and in the other after *l*-hyoscyamine (2·0 mg./kg.). In each case the dose of neostigmine was 0·4 mg./kg. It was found to have no effect on the slow activity induced by either of these drugs.

(ix) *Combinations of barbiturates, physostigmine and atropine.*—The effects of physostigmine on the electrical patterns induced by barbiturates were studied in five experiments. Pentobarbitone was used in three of these experiments and sodium amytal in the other two. In each case the barbiturate was given in a dose sufficient to produce moderate anæsthesia. With pentobarbitone the dose required was of the order of 30 to 35 mg./kg. by intraperitoneal injection. The characteristic "spindle burst" activity was then seen (fig. 6A). This usually ranged over a frequency of 10 to 15 c/s and was more prominent in areas of the cortex which were not primary sensory or motor. They were also present in the medial thalamic nuclei, and the caudate nucleus. After physostigmine sulphate (in doses of 0·1 to 0·2 mg./kg.) had been given intraperitoneally, the spindle bursts disappeared and the electrical activity was dominated by a continuous rhythmic activity at a frequency of 5 or 6 cycles per second. This appeared in all regions but was largest in amplitude in those areas in which the spindles had been most marked (fig. 6B). The frequency of this rhythmic activity was noticeably constant.

XUM

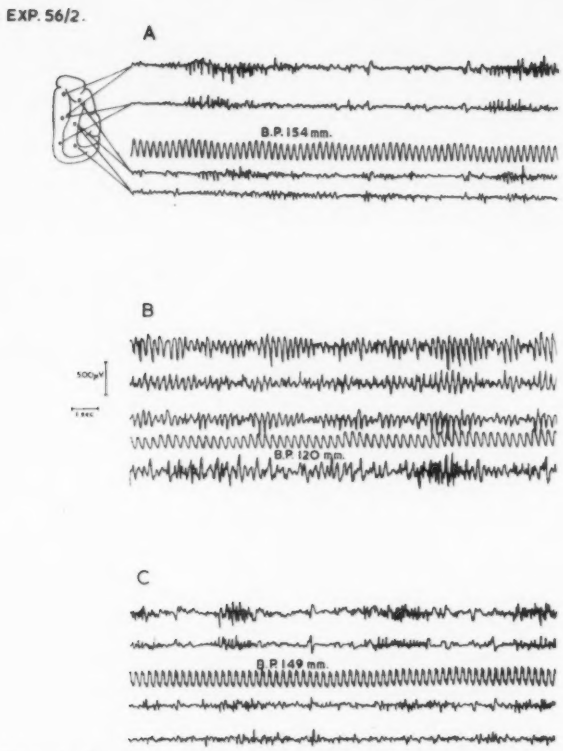


FIG. 6.—Records from an experiment in which physostigmine and atropine were given to a cat under pentobarbitone anæsthesia and in which blood pressure was also recorded. A, control record of pentobarbitone anæsthesia (30 mg./kg.); B, three minutes after the intravenous injection of 0·2 mg./kg. of physostigmine sulphate; C, two minutes after the subsequent injection of 1·0 mg./kg. of atropine sulphate.

In four experiments it was 6 per second, and in the other one 5 per second. The animal remained fully anæsthetized after physostigmine had been injected, and showed no sign of recovery. In two of these experiments physostigmine was followed by atropine sulphate in doses of 1·0 and 2·0 mg./kg. In both cases the continuous rhythmic activity disappeared within three minutes of the atropine injection, and the spindle bursts characteristic of barbiturate anæsthesia returned (fig. 6C). The animals made normal recovery from the anæsthetic.

(*b*) *In Acute Preparations. Encéphale isolé and cerveau isolé.*

The method by which these were prepared has been described. In the *encéphale isolé* the brain receives afferent impulses from the cranial

nerves only and the preparation shows periods of drowsiness or sleep which alternate with periods of wakefulness or apparent alertness, indicated by the behaviour of the eyes, ears and pupils (Bremer, 1936). The electrical activity of the cortex is different in these two states. In the waking state, in which movements of the ears and eyes, together with a pupillary response to light are seen, the electrical activity consists mainly of low amplitude fast activity in all regions, similar to that seen in the intact animal in the alert state (fig. 7B). In the sleeping

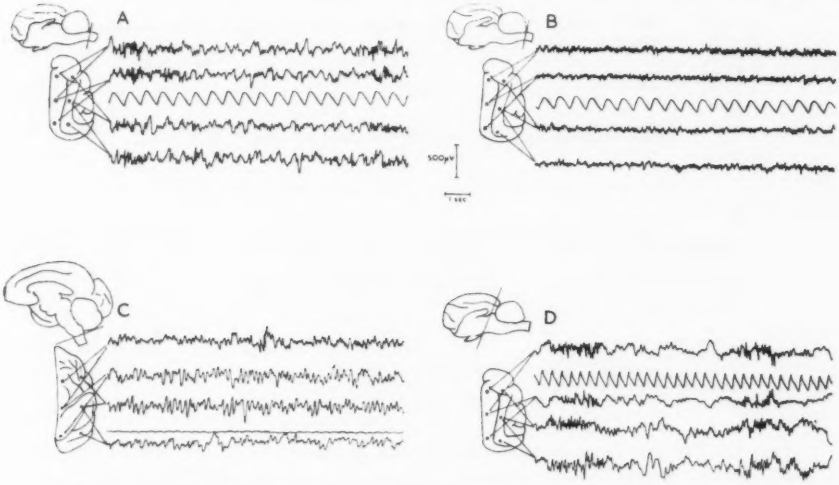


FIG. 7.—Normal records of acute preparations. A, *encéphale isolé* preparation (cat), "sleeping"; B, the same, "waking"; C, *encéphale isolé* preparation (monkey), "sleeping"; D, *cerveau isolé* preparation (cat).

state the eyes are rotated upwards and the pupil is fixed and constricted. The cortical activity in this state is dominated by bursts of spindle activity somewhat similar to those seen in the drowsy intact animal, and in barbitone anæsthesia, together with some slow activity (fig. 7A). The frequency range of the spindle activity is from 10 to 15 per second. When the *encéphale isolé* preparation is in the sleeping state it can still be roused by sensory stimulation, auditory stimuli (such as taps or clicks) being very effective in the cat. In the acute experiments in which monkeys were used, visual stimuli were also found to be effective.

In the *cerveau isolé* preparation the mid-brain is transected and this preparation has the appearance of being permanently asleep (Bremer, 1935). The eyes and ears no longer move and slow waves and spindle bursts are permanently present (fig. 7D). This preparation does not respond to afferent stimulation.

(i) *Physostigmine.*—In seven experiments in the *encéphale isolé* preparation, five of which were cats and two monkeys, physostigmine sulphate was given intravenously in doses of 0·1 to 0·5 mg./kg. In all seven experiments, the spindle and slow wave activity of the sleeping state was abolished after the drug had been given, and did not reappear (fig. 8B). No change in the behaviour of the preparation was, however,

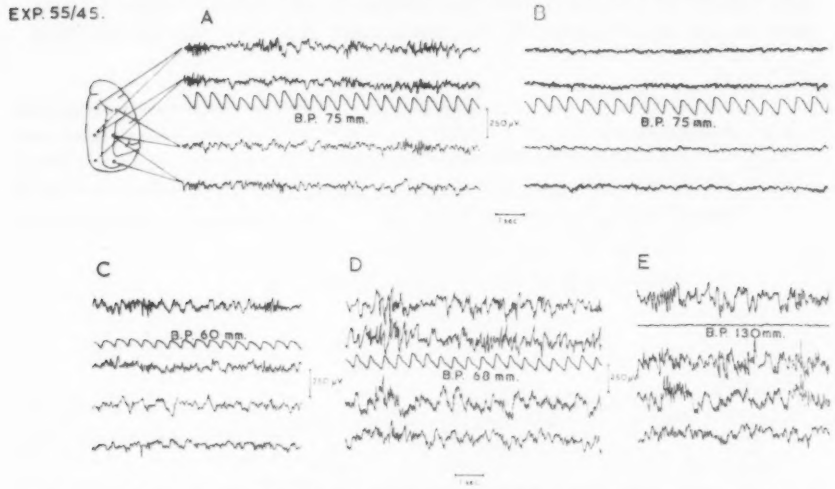


FIG. 8.—Records from an acute experiment (*encéphale isolé* cat preparation) in which blood pressure was recorded. A, control record with the preparation "sleeping"; B, forty seconds after 0·1 mg./kg. of physostigmine sulphate had been injected intravenously; C, five minutes after the subsequent injection of 2·5 mg./kg. of atropine sulphate; D, six minutes after a total dose of 4·0 mg./kg. of atropine had been given; E, sixty seconds after the intravenous injection of 2 μg. of *nor*-adrenaline showing the peak of the blood pressure rise.

observed. In all except one cat experiment blood pressure was recorded simultaneously with electrical activity. The slight blood pressure changes which occurred following physostigmine were transient, and the general level of blood pressure remained unchanged. (fig. 8B). The rate of respiration in these experiments was controlled artificially, and remained constant.

Physostigmine was given intravenously to the *cerveau isolé* preparation in four experiments in cats, the doses ranging from 0·1 to 0·5 mg./kg. Here, too, the spindle and slow activity was abolished and did not reappear (fig. 9B). In two of these experiments blood pressure was recorded simultaneously with the electrical activity. The changes in blood pressure which occurred were again transient, though the electrical effects persisted (fig. 9B).

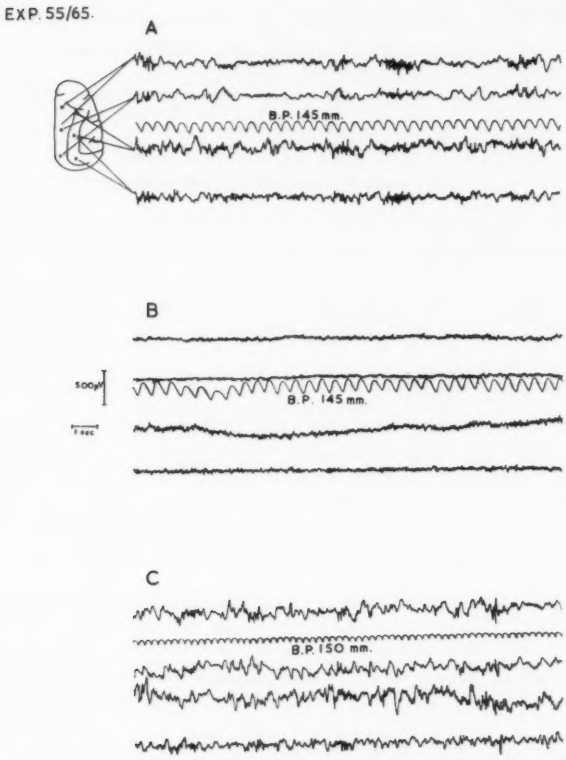


FIG. 9.—Records from an acute experiment (*cerveau isolé* cat preparation) in which physostigmine was followed by atropine. A, control record; B, three minutes after 0·1 mg./kg. of physostigmine sulphate had been injected intravenously; C, five minutes after the subsequent injection of 2·0 mg./kg. of atropine sulphate.

(ii) *Atropine and l-hyoscyamine.*—Atropine (1·5 to 4·0 mg./kg.) was given in four experiments to the *encéphale isolé* and *l*-hyoscyamine (2·0 mg./kg.) in one experiment. In each case the slow activity, similar to that seen in the conscious intact animal, was observed (fig. 10B). No changes in the behavioural state of the preparation were, however, seen, although in one case the drug was injected when the preparation was in the waking state. As was observed with physostigmine, the time course of the blood pressure changes following these drugs did not correspond to the changes in electrical activity (fig. 10B).

Atropine and *l*-hyoscyamine were not used in experiments in the *cerveau isolé* preparation except following the administration of physostigmine.



XUM

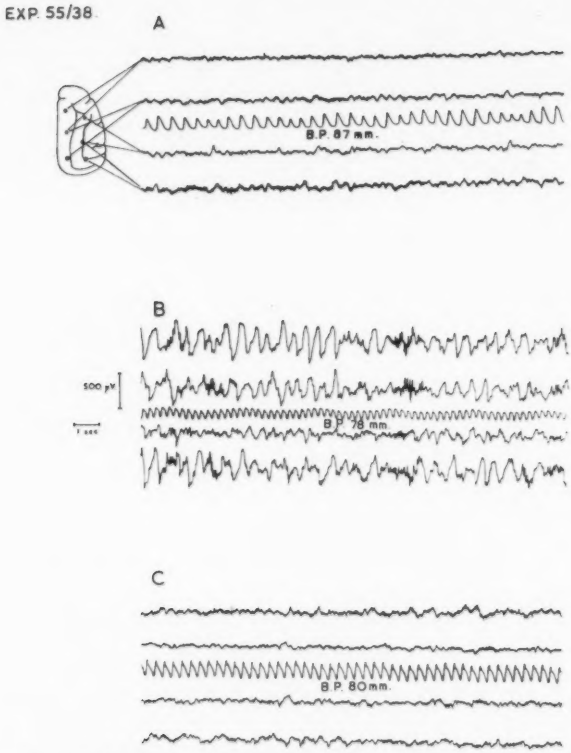


FIG. 10.—Records from an acute experiment (*encéphale isolé* cat preparation) in which atropine was followed by physostigmine. A, control record with the preparation "awake"; B, one and a half minutes after 2·0 mg./kg. of atropine sulphate had been injected intravenously; C, seven minutes after the subsequent injection of 0·4 mg./kg. of physostigmine sulphate.

In the acute experiments there was an antagonism between physostigmine and atropine (or *l*-hyoscyamine) similar to that observed in the experiments in the conscious animal, Thus when atropine or *l*-hyoscyamine was given after physostigmine, the effects of the latter were abolished. This was seen with atropine (2·0 to 5·0 mg./kg.) in four of the experiments in the *encéphale isolé*, and with *l*-hyoscyamine (2·0 to 4·0 mg./kg.) in two. The effect of a small dose of atropine (2·5 mg./kg. in fig. 8C) was to restore the spindle and slow activity of this preparation, whilst a larger dose (fig. 8D after 4·0 mg./kg.) caused the appearance of slow waves of high amplitude as seen when atropine was given alone. Very similar effects were observed in the two experiments in which *l*-hyoscyamine was used.

In the four experiments in the *cerveau isolé* in which physostigmine had been given, this drug was followed by atropine or *l*-hyoscyamine. The effects were similar to those seen in the *encéphale isolé*. In two experiments atropine (2·0 and 2·5 mg./kg.) was used, and in the other two *l*-hyoscyamine (2·0 and 4·0 mg./kg.). In all four the spindle and slow wave activity which had been abolished by the administration of physostigmine reappeared (fig. 9C).

Conversely, in the experiments in which atropine and *l*-hyoscyamine were injected intravenously into *encéphale isolé* preparations, it was noted that their effects could be subsequently blocked by physostigmine (fig. 10C) although in some cases larger doses were required (0·4 to 2·0 mg./kg.).

In two experiments with *encéphale isolé* preparations in which atropine had been given following physostigmine in a sufficiently large dose to cause the appearance of the irregular slow waves, the blood pressure had fallen slightly as compared with the level at the beginning of the experiment (fig. 8D). In these experiments an infusion of *nor*-adrenaline, given into the femoral vein, raised the blood pressure to a level considerably in excess of that observed previously; despite this, the character of the electrical activity remained unchanged, and the slow waves persisted (fig. 8E).

## III. The Effects of Sympathomimetic, Sympatholytic and Related Compounds on Electrical Activity and Behaviour

### (*a*) *In the Conscious Animal*

(i) *r-amphetamine*.—In eighteen experiments in the conscious preparations this drug was given, either alone, or preceded by other drugs. It was usually administered intraperitoneally in doses of 1·0 to 5·0 mg./kg., but in some experiments it was given orally in similar doses. Doses between 1·0 and 2·0 mg./kg. had little or no effect on electrical activity or behaviour, whereas doses between 2·0 and 5·0 mg./kg. regularly changed the electrical activity to the alert pattern, i.e. low amplitude, fast activity (fig. 11B). This change was seen in all regions of the cortex and in leads from both the medial and lateral thalamic nuclei, the hypothalamus and the caudate nucleus. At the same time the behaviour of the animals was altered. They appeared much more restless and alert. Very often they could be seen to explore the corners of the constant environment box in which they had not previously shown any interest. In some cases they showed excitement, involving circling movements and escape reactions. The pupils were dilated and the respiratory rate increased. In none of these experiments did the animals become drowsy or fall asleep after amphetamine had been given, and the electrical and behavioural effects of the drugs were still present after

XUM

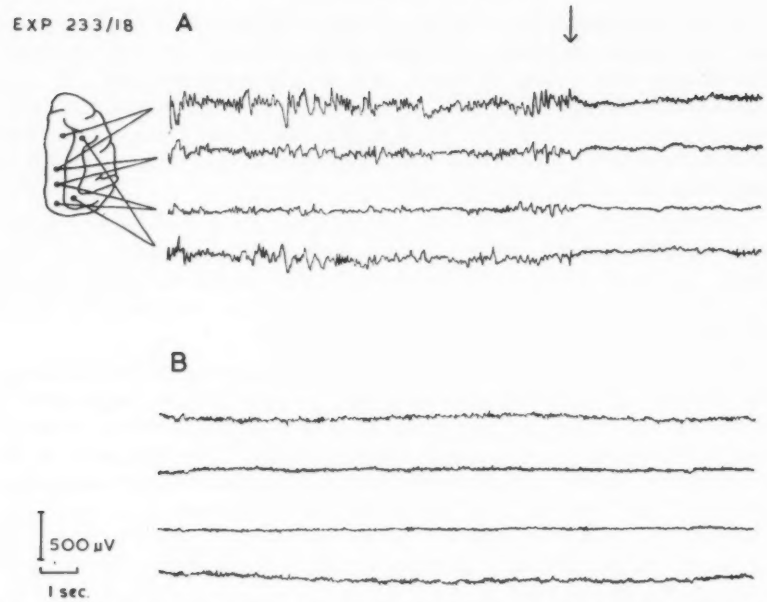


FIG. 11.—A, Control record of normal conscious cat with arousal response; B, twenty minutes after an intraperitoneal injection of 2·3 mg./kg. of *r*-amphetamine sulphate.

five or six hours. However, these effects usually wore off in twenty-four hours. Owing to the extreme restlessness of these animals after amphetamine it was often very difficult to obtain a recording of the electrical activity which was free from movement artefacts.

*r*-amphetamine also had an effect on the amplitude of the cortical response to rhythmic photic stimulation. When photic stimulation was applied to the normal animal, using an electronic stroboscope lamp which was arranged to give flashes of light at regular intervals, it was possible to record from the primary visual area in the conscious animal a rhythmic response at the same frequency as the stimulus (fig. 12A). The response was always in the form of a wave and was not a discrete response to each flash, provided the frequency of stimulation was above 4 flashes per second. If the stimulus was maintained, it was found that the response had a steady amplitude and that this did not vary appreciably with the position of the animal relative to the stroboscope lamp (the walls of the constant environment box, being light in colour, gave good reflection of the flash). It was therefore thought that changes in the amplitude of the response were not likely to be due to changes in the position of the animal, though, where the responses were being measured,

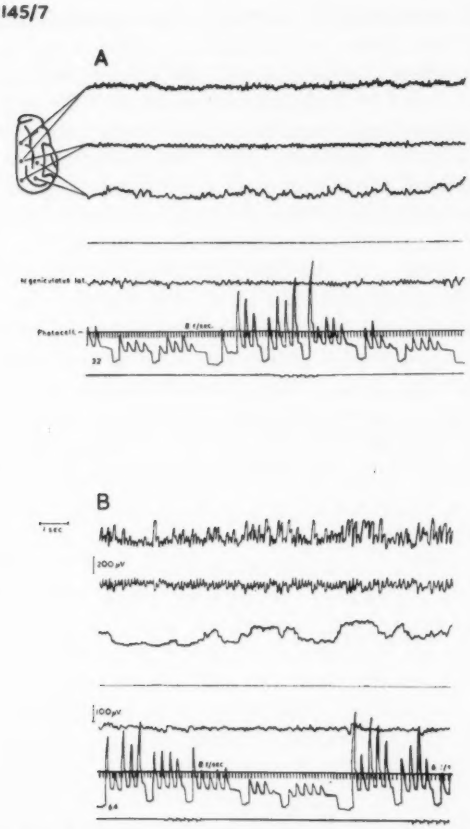


FIG. 12.—Records of the response recorded from the visual cortex to rhythmic photic stimulation. A, in the normal conscious animal; B, after 4·0 mg./kg. of *r*-amphetamine sulphate (intraperitoneally). In record B the gain of the wave analyser has been reduced by one-half.

they were checked as far as possible with the animal in the same position. Changes in the amplitude of the response with changes in the behavioural state of the animal were, however, observed. When the stroboscope lamp was first switched on it usually alerted the animal and the maximum response was then obtained. If the lamp was then left on, the animal sometimes remained alert, but very often, after a while, lapsed into a quiet or drowsy state and the amplitude of the response then diminished. It could be restored by switching the lamp off and on again. Thus the best assessment of the response to photic stimulation at different frequencies was obtained by switching on the lamp at each frequency to be

XUM

examined, and measuring the response after a given time interval in each case.

A cortical response to photic stimulation was observed at all frequencies between about 4 and 25 cycles per second and if the stimulus frequency was varied continuously between these limits, the frequency of the response followed in the same way. With stimulation at frequencies below 4 per second there was usually a discrete response to each flash of light. The amplitude of the rhythmic response was usually greatest at the lower frequencies and decreased progressively as the stimulus frequency increased. In the normal animal the response was usually too small to be measured above 25 flashes per second.

After 3·0 to 5·0 mg./kg. of *r*-amphetamine, this rhythmic response was increased in amplitude, particularly at frequencies between three and ten per second (fig. 12B). This is illustrated in fig. 13, in which the amplitude of the response recorded from the visual cortex has been plotted against frequency in one of these experiments. The amplitude at the lower frequencies was more than doubled after amphetamine and

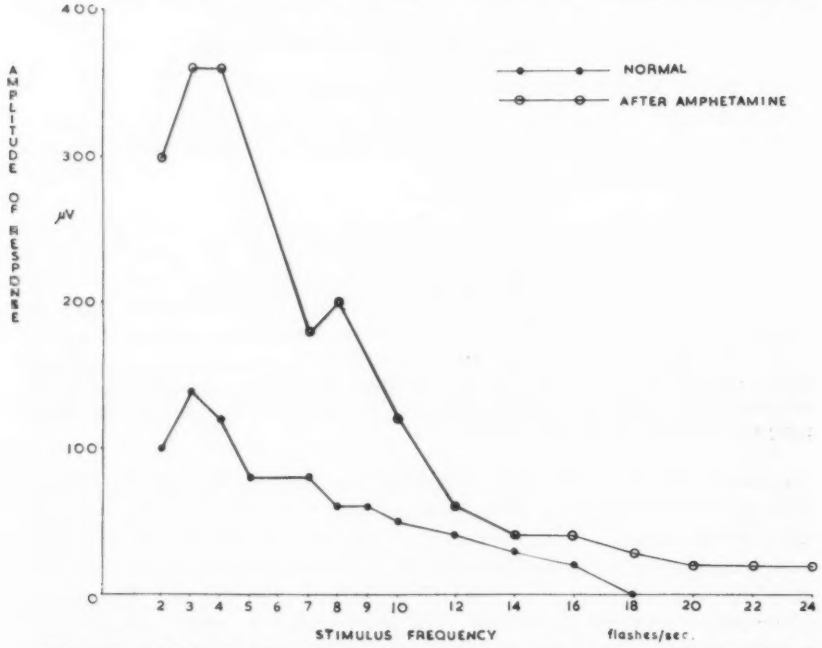


FIG. 13.—Graph showing the amplitude of the response to rhythmic photic stimulation recorded from the visual cortex in the conscious animal, plotted against the frequency of stimulation. A, in the normal animal; B, after 4·0 mg./kg. of *r*-amphetamine sulphate.

at higher frequencies a response could be detected up to 24 flashes per second. Similar curves were obtained in the other experiments but in some cases the restlessness of the animals after amphetamine made it difficult to measure the responses accurately.

Since amphetamine also caused dilation of the pupils, the effect of this on the photic response had to be checked. In two experiments the eyes were treated with a 5 per cent solution of cocaine until the pupils were fully dilated and the control recording was then taken. In these experiments, the increase in the photic response was still obtained after the administration of *r*-amphetamine.

(ii) *d-amphetamine.*—Experiments on four animals with this substance showed that in similar doses it had the same effect on electrical activity and behaviour as did *r*-amphetamine.

(iii) *l-amphetamine.*—This was used in four experiments and was found to have similar effects to *r*-amphetamine but larger doses (10 to 15 mg./kg.) were required.

(iv) *Combinations of r-amphetamine and other substances.*—Since amphetamine was found to produce alerting of electrical activity, and of behaviour, its effect on the states induced by barbiturates and on the slow activity induced by atropine were tested:

(1) *Barbiturates.*—In three experiments, sodium amytal, thiopentone and dial were used respectively, and were given in doses sufficient to produce a state of moderately light anæsthesia. *r*-amphetamine was then administered in increasing doses. It was found that even with large doses (20 mg./kg.), amphetamine had no effect on the depth of anæsthesia, or on the electrical patterns induced by the barbiturates.

In one experiment, a large initial dose of *r*-amphetamine (20 mg./kg.) was followed by thiopentone. A normal dose of thiopentone (20 to 25 mg./kg.) was required to produce anæsthesia and the alert pattern of electrical activity was replaced by the spindle burst activity of barbiturate anæsthesia.

(2) *Atropine.*—In three experiments in the conscious preparations, in which *r*-amphetamine had been given in doses of 3·0 to 5·0 mg./kg. and alerting of electrical activity and of behaviour had been produced, atropine sulphate was given in doses of 2·0 to 3·0 mg./kg. In each case the premedication with amphetamine did not prevent the appearance of the slow wave activity after atropine, and the usual dose of the latter drug was sufficient to produce this activity. However, behaviourally the animal remained in the excited or hyperactive state induced by amphetamine. In another series of three experiments the order of the drugs was reversed, atropine (2·0 to 3·0 mg./kg.) being given first, followed by *r*-amphetamine (3·0 to 5·0 mg./kg.). The latter did not modify the slow wave activity, although the animals became excited in the usual way.

XUM

(v) *Mescaline*.—Eight experiments were carried out with this drug, which was given either by mouth or intraperitoneally in doses between 10 and 25 mg./kg. No change in electrical activity or behaviour were observed with these doses. In two other experiments larger doses (50 mg./kg.) were used, and in these vomiting and defæcation occurred within thirty minutes of the drug being given. The vomiting went on at intervals for about one hour, and during this time the electrical activity tended towards the alert type of pattern, as the animals were becoming restless. About an hour and a half after the mescaline had been given, the animals passed into a stuporous state, in which they lay taking little notice of the environment. In this state, the electrical activity was dominated by rhythmic waves at 4–6 c/s from all areas (fig. 14C), although this activity was more prominent in areas of the cortex not

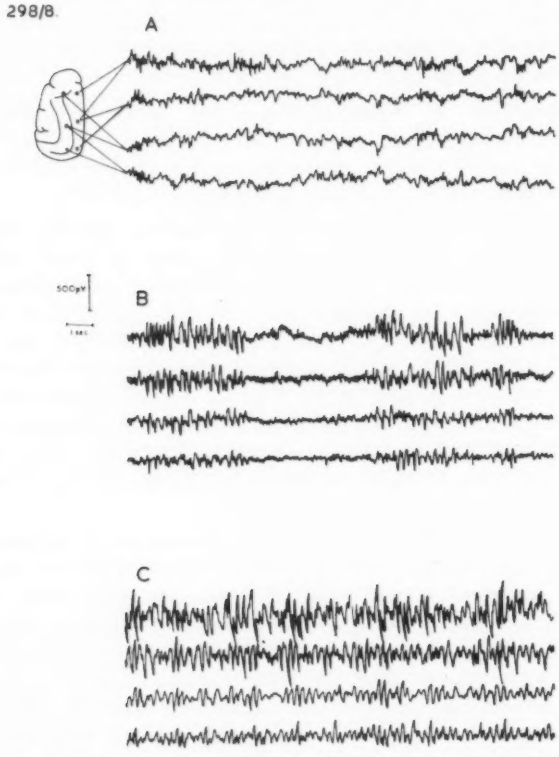


FIG. 14.—Records from an experiment in which a large dose of mescaline was given to a conscious animal. A, control record of normal animal in drowsy state; B, eighteen minutes after 50 mg./kg. of mescaline sulphate had been injected intraperitoneally; C, two hours after the administration of mescaline.

primary sensory or motor. Whilst the animals were in this state, they did not respond to the usual sensory stimuli (e.g. noise or light) nor did the electrical activity change. Handling, however, did rouse the animals, and they would then move about for a while before relapsing into the stuporous state. During this active period the electrical activity changed to the alert pattern.

Mescaline was not used in combination with any other drugs.

(vi) *Lysergic acid diethylamide* (LSD 25).—This drug was used in eighteen experiments, either alone or preceding other drugs in the conscious animal. The doses were between 7·5 and 100 μg./kg. Doses of less than 15 μg./kg. appeared to have no effect on electrical activity or behaviour. Doses of 15 to 25 μg./kg. were observed in an early series of eight experiments to produce similar changes in electrical activity to those seen with amphetamine, although the change was not always so marked. Thus there was a tendency towards the alert type of activity, but some rhythmic activity often remained, although its amplitude was small and the frequency relatively high (15 to 20 c/s) (fig. 15B). The animals were always more restless and alert after these doses of LSD 25. In a later series of experiments in which slightly larger doses of LSD 25

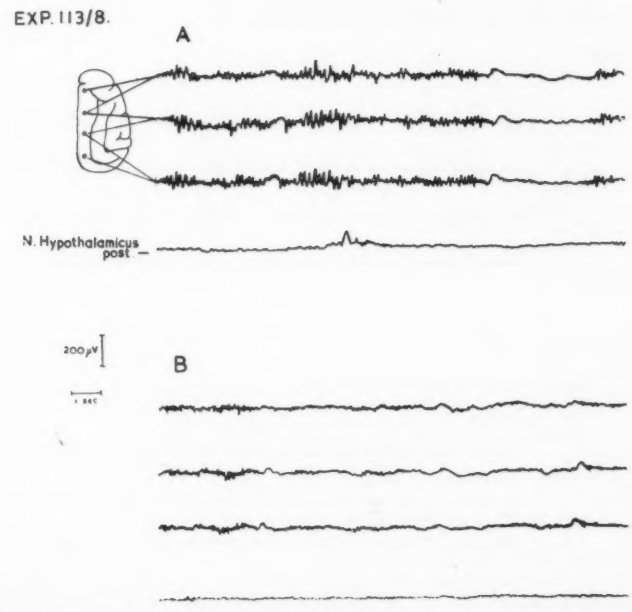


FIG. 15.—A, Control record of normal conscious cat in quiet state; B, twenty minutes after an intraperitoneal injection of 15 μg./kg. of LSD 25.

were used (35 to 43 μg./kg.), somewhat different electrical effects were observed. Here more rhythmic activity was present in the record. This activity usually occurred in bursts, at a frequency between 4 and 7 c/s. It could be blocked by sensory stimulation in the same way as the rhythmic activity of the normal animal Similar changes in behaviour to those seen in the previous series of experiments were observed.

In this later series, the experimental conditions had been changed slightly inasmuch as the constant environment chamber had been moved into a sound-proofed room. The possible significance of this factor and the differences in the results in the two series of experiments in relation to the possible mode of action of this drug are discussed below.

No change in the cortical response to photic stimulation was observed following administration of LSD 25.

(vii) *Combinations of LSD 25 and other drugs.*—(1) *Barbiturates.*—In three experiments LSD 25 was given following administration of barbiturates in doses sufficient to produce a state of moderately light anæsthesia (fig. 16A). Pentobarbitone was used in two experiments and sodium amytal in the third. When LSD 25 was given in doses between 100 and 150 μg./kg., the characteristic spindle burst activity of the barbiturate anæsthesia disappeared (fig. 16B). This activity did not reappear, although the depth of anæsthesia was unaltered, and recovery

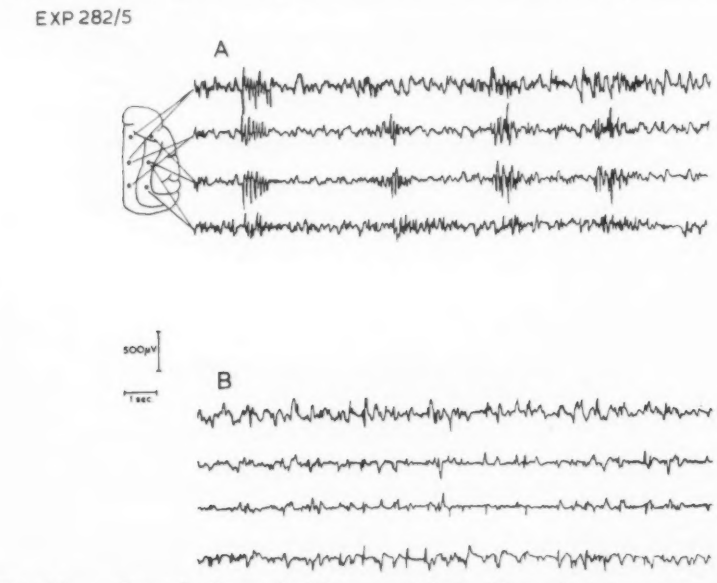


FIG. 16.—A, Record of pentobarbitone anæsthesia (30 mg./kg.) in a cat; B, four minutes after 100 μg./kg. of LSD 25 had been injected intravenously.

from the anæsthetic was normal. In one of these experiments LSD 25 was followed by an intravenous injection of 2·0 mg./kg. of SKF 688, an adrenaline blocking agent. This drug had no effect on the electrical activity, and did not restore the spindling. In another series of three experiments, LSD 25 was administered in doses of 100 to 150 μg./kg. and then followed by sodium amytal. Although the usual dose of amytal produced anæsthesia, the spindle burst activity never appeared.

(2) *Atropine and l-hyoscyamine.*—In two experiments, atropine sulphate (3·0 and 3·3 mg./kg.) and in one experiment, *l*-hyoscyamine (2·0 mg./kg.) were administered before LSD 25. Although in each case the dose of LSD 25 was increased to 100 μg./kg., no change in the electrical pattern

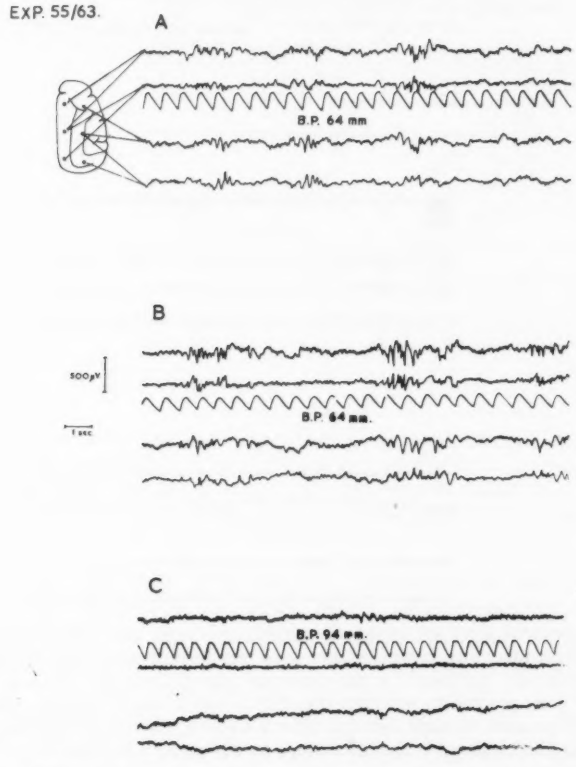


FIG. 17.—Records from an acute experiment (*encéphale isolé* cat preparation) where LSD 25 was followed by *r*-amphetamine A, control record with the preparation "sleeping"; B, three minutes after 35 μg./kg. of LSD 25 had been given intravenously showing no effect on the electrical activity or blood pressure; C, two minutes after the subsequent intravenous injection of 1·0 mg./kg. of *r*-amphetamine sulphate.

of slow waves induced by atropine or *l*-hyoscyamine was observed. In every case, however, the animals became more restless and alert.

(*b*) *In Acute Preparations. Encéphale isolé and cerveau isolé*

(i) *Amphetamine*.—In thirteen experiments in the *encéphale isolé* preparation (eleven in cats and two in monkeys), *r*-amphetamine was injected intravenously in doses of 1·0 to 3·0 mg./kg. (figs. 17c, 18c and

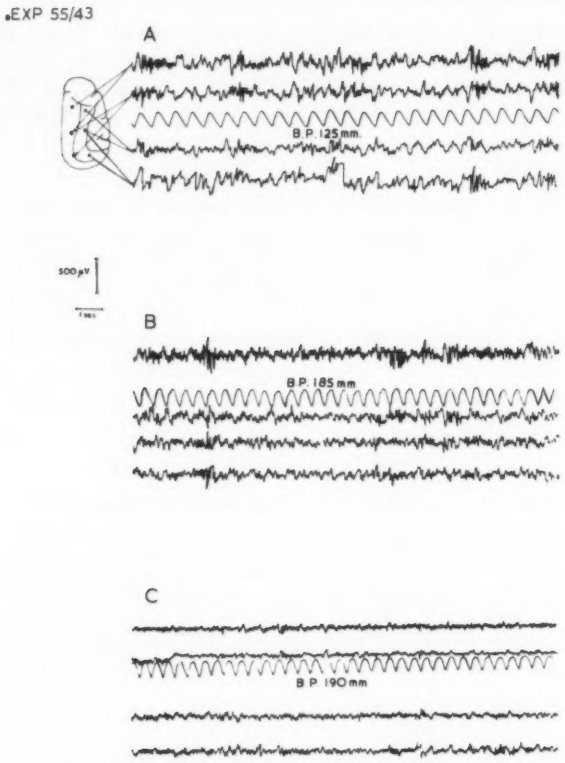


FIG. 18.—Records from an acute experiment (*encéphale isolé* cat preparation) in which *r*-amphetamine was given initially in a very small dose. A, control record with the preparation "sleeping"; B, nine minutes after 0·2 mg./kg. of *r*-amphetamine sulphate had been given intravenously showing a rise in blood pressure; the spindle bursts are still present; C, eight minutes after 2·0 mg./kg. of *r*-amphetamine showing alerting of the EEG with little further change in the blood pressure.

19c). In all cases the spindle and slow activity was abolished, and did not reappear. The preparations also showed behavioural signs of arousal, i.e. the eyes opened and moved, and the pupils responded to light. In some cases, movements of the ears, jaw and vibrissæ were

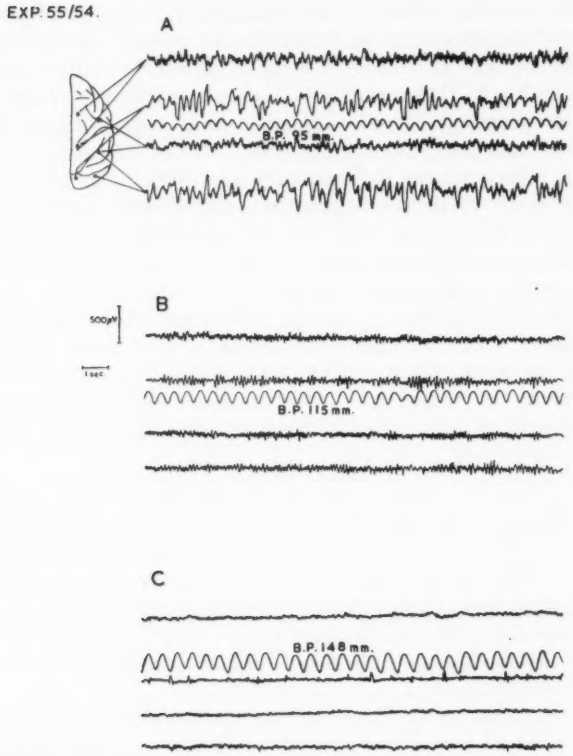


FIG. 19.—Records from an acute experiment (*encéphale isolé* monkey preparation) in which LSD 25 was given first and followed by *r*-amphetamine. A, control record with the preparation "sleeping"; B, three minutes after 20 μg./kg. of LSD 25 had been injected intravenously; C, one minute after the subsequent injection of 1·5 mg./kg. of *r*-amphetamine sulphate intravenously.

noted. In six cat, and both monkey preparations, blood pressure was recorded from the carotid artery simultaneously with the electrical activity. A rise in blood pressure occurred following the injection of amphetamine and this was maintained throughout the experiment. In two experiments, therefore, smaller quantities of amphetamine (0·2 and 0·5 mg./kg.) were injected initially. These doses were sufficient to produce a blood pressure rise (fig. 18B), together with a temporary blocking of the spindle activity. The latter, however, returned after about half a minute, whilst the higher level of blood pressure was maintained. A second injection of a larger quantity of amphetamine (1·0 to 2·0 mg./kg.) was then given, and the spindling abolished completely and permanently without further blood pressure

XUM

change. The alerting effects of amphetamine in this type of preparation did not therefore appear to be related to its general circulatory effects.

Amphetamine was also used in eight experiments in the *cerveau isolé* preparation. Six of these were cats and two monkeys. Three of these (cats), were prepared from *encéphale isolé* preparations to which amphetamine had already been given, causing alerting of electrical activity and behaviour, as described above. When the mid-brain transection was made in these preparations, the spindle and slow activity, characteristic of the *cerveau isolé* (fig. 7D) appeared. This activity could not be abolished by further injections of amphetamine, although doses up to 20 mg./kg. were used. At the same time, the eyes and pupils became fixed and showed no change following further administrations of amphetamine. All the other *cerveau isolé* preparations were prepared by the later method, using suction, and without the spinal cord being sectioned first. In these, too, amphetamine was found to have no effect on electrical activity or behaviour, although doses as high as 50 mg./kg. were used.

(ii) *LSD* 25.—This drug was used in two experiments in *encéphale isolé* (cat) preparations, and in two experiments in *cerveau isolé* (cat) preparations. No effects on either electrical activity or behaviour were observed in these experiments, despite high doses (up to 300 μg./kg.). In the two *encéphale isolé* preparations the administration of LSD 25 (fig. 17B) was followed by an injection of amphetamine (1·0 mg./kg.). An alerting of electrical activity (fig. 17C) and of behaviour was obtained following this drug.

In the three experiments in which monkey *encéphale isolé* preparations were used, LSD 25 was found to exert some effect on electrical activity. The monkey preparation was characterized by slow and intermittent rhythmic activity (figs. 7C and 19A) rather than by the spindle activity seen in the cat. Following LSD 25, given intravenously in doses of 20 to 30 μg./kg., this activity was replaced by bursts of rhythmic activity at a frequency of 7 to 8 c/s, waxing and waning in amplitude (fig. 19B). This change could be interpreted as a partial alerting of cortical activity, but no change in behaviour was noted. In one of our experiments, 1·5 mg./kg. of amphetamine was given subsequently. All rhythmic activity was then abolished (fig. 19C).

## Discussion

The above experiments, the results of which are summarized in Table II, allow a preliminary grouping of the effects of the drugs investigated, and some tentative conclusions as to their likely mode of action. It will have been observed that the correlation between the effects on electrical activity of the brain and on behaviour was closer in the case of some drugs than in others. This serves to emphasize the need for recording electrical activity

TABLE II

| | *Conscious animal* | | | |
|---|---|---|---|---|
| *Drug* | *Behaviour* | *Electrical activity* | *Electrical activity of encéphale isolé* | *Electrical activity of cerveau isolé* |
| Physostigmine | Normal | Fast, low amplitude activity | Fast, low amplitude activity | Fast, low amplitude activity |
| Atropine or *l*-hyoscyamine | Normal or excited | Slow waves and spindles | Slow waves and spindles | Slow waves and spindles |
| Amphetamine | Excited | Fast, low amplitude activity | Fast, low amplitude activity | No effect |
| LSD 25 | Excited | Fast, low amplitude activity | No effect | No effect |

simultaneously with behaviour, and hence, for studying wherever possible, the effects of drugs in suitable chronic, as well as in acute preparations.

In the conscious animal amphetamine produced low voltage fast electrical activity, and excitement (Bradley and Elkes, 1953*a*). This is in agreement with the observations of Shallek and Walz (1953) who noted that *d*-amphetamine, given to unanæsthetized dogs, caused an increase in motor activity and an increase in the frequency of the EEG. The effects of LSD 25 were somewhat similar. In our experiments this drug brought about behavioural alerting of the conscious animal, and a corresponding change in the electrical activity. Unlike amphetamine, however, the extent of these changes varied with the precise experimental conditions, the animal under LSD 25 being strikingly susceptible to environment, and to slight changes in it.

Physostigmine produced an electrical pattern similar to that seen in the alert state; but here (provided small doses were used) no corresponding change in behaviour could be observed. Atropine and *l*-hyoscyamine produced rhythms similar to those seen in sleep. In no case, however, were sleep or drowsiness noted, and occasionally atropine led to excitement. This dissociation between behaviour and electrical activity following atropine was first pointed out by Wikler (1952) who recorded "sleep patterns" in unanæsthetized dogs showing excitement after the administration of the drug. Funderburk and Case (1951) reported corresponding changes in the curarized cat preparation. They were, however, unable to determine whether the slow waves they observed were due to normal sleep, or the effects of atropine. More recently Rinaldi and Himwich (1955*a*) working with the curarized rabbit preparation and using atropine and an anticholinesterase (DFP) have reported similar effects on electrical activity. Again, however, the experimental conditions precluded observation of behaviour.

XUM

Neostigmine in our experiments did not have any effect on electrical activity even in relatively high doses. *l*-Hyoscyamine caused effects similar to atropine, while *d*-hyoscyamine was ineffective. The lack of effect of neostigmine is in agreement with its lack of effect in the spinal cord (Schweitzer, Stedman and Wright, 1939), although, using this drug, Bremer and Chatonnet (1949) noted a reduction in voltage and increase in frequency in the electrocorticogram of the *encéphale isolé* preparation.

The drugs used in our experiments thus fall into two distinct groups: those which affected activity and behaviour in the same way (the amphetamines and LSD 25) and those which produced effects on electrical activity which did not result in a corresponding change in behaviour (physostigmine, atropine and *l*-hyoscyamine). Furthermore, wherever combinations of drugs from these two groups were employed, the behavioural effects appeared to be dominated by members of the first group (amphetamine and LSD 25) and the electrical effects by members of the second (physostigmine, atropine and *l*-hyoscyamine). Thus, for example, when atropine was given following *r*-amphetamine, the animals remained excited and hyperactive, but the slow wave activity attributable to atropine invariably appeared; nor could this activity be abolished by amphetamine if the order of the drugs was reversed, despite the fact that amphetamine still produced its characteristic effects on behaviour.

The acute preparations allowed only very limited observations of behavioural change. Within these limits, however, the distinction between the two groups of drugs was maintained. When amphetamine was administered intravenously to the *encéphale isolé* preparation, both behavioural and electrical alerting could be observed. Physostigmine, atropine and *l*-hyoscyamine on the other hand, produced their characteristic electrical effects without behavioural change, and here, too, dose level was found to be important. A small dose of physostigmine would produce a change in electrical activity without a change in behaviour. A larger dose did produce behavioural alerting, which, however, was always accompanied by some peripheral signs, such as salivation. The predominance of the behavioural effects of amphetamine and the electrical effects of atropine could still be seen in the *encéphale* preparation, since, when amphetamine was administered first, and followed by atropine, the preparation remained behaviourally alert, but the electrical activity showed the slow waves usually associated with atropine.

The *encéphale isolé* served one further purpose. By recording blood pressure simultaneously with electrical activity, it could be shown that the central effects of the drugs studied were not related to changes in systemic blood pressure. Thus, although *r*-amphetamine caused a rise in blood pressure, this effect could be produced with a dose much smaller than that required to cause alerting. Similarly, the slow activity induced by atropine did not depend on the fall of blood pressure sometimes seen in

these experiments, since the blood pressure level could be restored, or even raised above its original level, by an infusion of *nor*-adrenaline without affecting the electrical pattern in any way. These observations, however, have no bearing on a possible effect of the drugs on *local* cerebral vascular tone and on local cerebral circulation. The possibility of such effects must be very clearly borne in mind.

In the *cerveau isolé* preparation similar effects on electrical activity were observed with physostigmine, atropine and *l*-hyoscyamine; here, too, the effects could not be related to blood pressure changes, which were recorded in all the later experiments.

The distinction between the two groups of drugs is still further emphasized by a new and different factor, namely, the effect of the plane of section on the response of the electrical activity to the drug under investigation. Thus, physostigmine, atropine and *l*-hyoscyamine still produced their characteristic effects on the electrical activity irrespective of whether the brain was transected at the level of the spinal cord (*encéphale isolé*) or

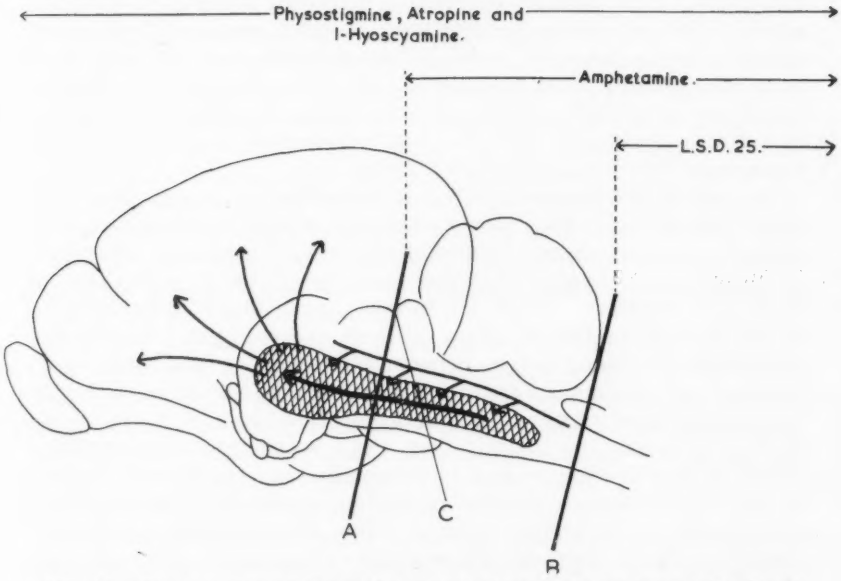


FIG. 20.—Diagram through the medial sagittal plane of the cat brain (after Starzl, Taylor and Magoun, 1951*b*), showing the reticular activating system of the brainstem (cross-hatched) its afferent collaterals from the sensory pathways and ascending influence on the diencephalon and cortex. "A" indicates the plane of transection of the mid-brain for the *cerveau isolé* and "B" the level of section of the spinal cord for the *encéphale isolé*. "C" is the plane which was found by Bonvallet *et al.* (1954) to be critical for the arousal produced by adrenaline. The susceptibility of the various preparations to the drugs mentioned in the text is indicated.



XUM

at the level of the superior colliculus (*cerveau isolé*). These drugs also affected the barbitone anæsthetized preparation. On the other hand, amphetamine, while exerting an effect on the intact animal and on the *encéphale isolé*, had no effect on the *cerveau isolé;* and, in the cat, LSD 25 exerted no effect on either of the acute preparations (fig. 20). It did, however, affect the activity seen in barbiturate anæsthesia.

These results, together with the recent studies of Rinaldi and Himwich (1955*a*), confirm our previous findings (Bradley and Elkes, 1953*a* and *b*). They also extend these findings to other species. Our own experiments included six monkeys. Rinaldi and Himwich studied the effect of drugs on spontaneous and evoked activity in the curarized rabbit. They observed that DFP led to persistent low voltage fast activity, whereas atropine "evoked an EEG pattern of sleep," and "inhibited all alerting reactions produced by physiological stimuli and the direct stimulation of the mid-brain reticular substance." They also noted that the alerting of the electrocorticogram by DFP was not prevented by transection of the mid-brain. These authors observed a transitory alerting of electrical activity following intracarotid injections of small amounts (0·5–15 $\mu$g.) of acetylcholine in both the intact curarized rabbit, and following mesencephalic section. This is in keeping with the observations of Bonnet and Bremer (1937) who used the *encéphale isolé* preparation, and with our own observations on the *encéphale isolé*, *cerveau isolé*, and the barbiturate anæsthetized preparation (Bradley, 1953).

The similarities between DFP and physostigmine suggest that their effects may be due to their anticholinesterase activity, and therefore to an endogenous accumulation of acetylcholine, or a related ester. The effects of atropine and *l*-hyoscyamine may similarly be due to a blockade of cholinergic receptors. There are, however, two differences between the central and the peripheral effects of these drugs. Firstly, the mutual antagonism in central action between physostigmine and atropine or hyoscyamine is maintained despite relatively high doses of either; secondly, whereas the doses of physostigmine required to produce effects on the electrocorticogram are smaller than those which produce peripheral effects, those of atropine and *l*-hyoscyamine are considerably higher. Despite these differences it seems probable that the central effects of these drugs involve a cholinergic pathway within the central nervous system (Feldberg, 1951). Since the effects of these drugs could still be observed after mesencephalic section, it seems unlikely that these receptors are localized below the level of the section. Equally, the lack of correlation between the effects on electrical activity and behavioural effects in the conscious animal suggests that a cholinergic mechanism is unlikely to be dominant in the mechanisms concerned with wakefulness and arousal.

On the other hand, the effects of amphetamine which produced both the behavioural and electrical signs of arousal, were susceptible to

XUM

mesencephalic section. The work of Moruzzi and Magoun (1949), Lindsley *et al.* (1949 and 1950) and Starzl *et al.* (1951*a* and *b*) has defined the role played by the reticular formation and tegmentum of the lower brain-stem in the electrical and behavioural arousal response, and the maintenance of wakefulness. As is well known, in their hands, electrical stimulation of this region produced the electrocortical signs of arousal (Moruzzi and Magoun, 1949). Lindsley *et al.* (1949 and 1950) noted that acute lesions in this region blocked the effects of stimulation, whilst chronic lesions in the same area led to somnolence and to slow waves in the EEG which could be only transitorily blocked by afferent stimuli. The work of Starzl *et al.* (1951*a* and *b*) has suggested that the activity in this region is maintained by impulses reaching it by way of medial collaterals from the main sensory pathways. When relating our own findings with amphetamine to those of Magoun, Moruzzi *et al.* (fig. 20), two aspects seemed of interest. First, the behavioural arousal following amphetamine was, like the one following stimulation of the reticular activating system, accompanied by desynchronization of the electrocortical activity; and second, the behavioural and electrical effects of the drugs were apparently dependent on intact mesencephalic connexions. This led to the suggestion that the effect of this drug might be exerted on receptors related to, or possibly located in, the brain-stem reticular activating system (Bradley and Elkes, 1953*a*). The recent results of Hiebel *et al.* (1954) are in keeping with this suggestion. They studied the effect of *d*-amphetamine in curarized preparations subjected to lesions at various levels, and found the critical level of section for this drug was somewhat higher than our own. However, in these experiments the electrocortical activation produced by the drug, rather than the behavioural effect, served as criteria of arousal.

The alerting effect of LSD 25 in the cat was lost following section of the spinal cord at the level of the first cervical vertebra. On the other hand, in the monkey it could still be seen following high spinal section, though this was not as marked as the alerting seen following amphetamine. Unfortunately, it was not possible to determine whether a high level of section would abolish this effect in the monkey. LSD 25, however, had no effect on the *cerveau isolé* preparation in the cat.

In the conscious cat the degree of alerting obtained with LSD 25 was rather variable and seemed to be dependent on slight variations in the environment. Thus, for example, in early experiments where the animal was placed in the constant environment chamber and housed in the open laboratory, almost complete alerting of the electrical activity was regularly obtained. Here, some noise must have got through the walls and the openings of the box. When in later experiments, the constant environment box was placed in a rigorously sound-proofed room, the degree of alerting of electrical activity was strikingly reduced and some rhythmic

XUM

activity at 4–6 c/s could be seen in many experiments. Similarly, in one of the *encéphale isolé* experiments in the monkey in which a small portion of the spinal cord had escaped section, more complete alerting was observed than in those experiments where the transection was complete. The alerting produced by amphetamine on the other hand was seen regularly, appeared independent of environment, and depended on dosage only. The effects of *r*-amphetamine in producing an increase in the cortical response to rhythmic photic stimulation in the conscious animal may be related to its alerting effects.

It would thus seem possible that whereas amphetamine may affect some element in the reticular activating system directly, the effect of LSD 25 may be exerted on other elements more closely related to the inflow of medial collaterals from the great afferent pathways. The activation of the symptoms of LSD 25 intoxication by sensory stimulation (Bradley, Elkes and Elkes, 1953) and the sequence of development of symptoms observed in typical LSD 25 intoxication, where sensorium and body image are affected well before motor involvement, are in keeping with this view.

The experiments outlined above suggest the existence of two or possibly three types of receptors within the central nervous system. One is almost certainly cholinergic in nature and its activation or blockade leads to effects on electrical activity which, in the conscious animal, are not necessarily related to behaviour. Rinaldi and Himwich (1955*b*) concluded that the alerting of electrical activity obtained with DFP and acetylcholine was due to an action on the reticular activating system at the mesencephalic level, and that atropine was a "specific depressant of that system." This was suggested to them by the fact that the slow, atropine-induced electrical activity could not be abolished by sensory stimulation, or stimulation of the mid-brain reticular activating system. In our experiments in the conscious animal receiving atropine, not only was behaviour unaffected, but sensory stimulation produced a normal behavioural response despite persistent high voltage slow activity. It is therefore difficult to accept the view that the reticular activating system is preponderantly cholinergic in nature, though a cholinergic element may well be represented in that area, and is almost certainly dominant in the pathways leading rostrally from the reticular formation towards the cortex. It may in fact be that the diffuse thalamic projection system (Jasper, 1953) may hold such an element, and that it is the effect on these receptors which produces effects on electrical activity without necessarily producing changes in behaviour. Equally, as mentioned above, cholinergic receptors may well be important in regulating local cerebral vascular tone.

The non-cholinergic receptors susceptible to amphetamine may be situated at a fairly high level of the brain-stem reticular formation. The recent work of Bonvallet, Dell and Hiebel (1954) stressing the importance

XUM

of adrenaline in the function of facilitatory and inhibitory mechanisms would certainly be in keeping with the suggestion. Both *nor*-adrenaline and adrenaline have recently been identified in the upper brain-stem (Vogt, 1954). The central action of amphetamine may be due to an action on receptors in this area, though the precise relation to the peripheral sympathomimetic action of the drug must remain an open question.

LSD 25 may act on receptors at the mesencephalic and diencephalic levels specially related to the medial collaterals of the great afferent pathways. The presence of serotonin in the brain (Amin, Crawford and Gaddum, 1954), the chemical relationship between LSD 25 and serotonin (Woolley and Shaw, 1954) and the antagonism between LSD 25 and serotonin (Gaddum, 1953), make the existence of receptors for tryptamine derivatives in the central nervous system likely. It is, however, difficult in the light of recent evidence (Cerletti and Rothlin, 1955; and Bradley and Hance, 1956) to accept the view that the effect of LSD 25 is due solely to its serotonin antagonism.

Perhaps rather than thinking in unitary terms, it may, at this stage, be advisable to think in terms of the possible selection by chemical evolution of small families of closely related compounds, which by mutual interplay would govern the phenomena of excitation and inhibition in the central nervous system. Acetylcholine, *nor*-adrenaline and 5-hydroxytryptamine may be parent molecules of this kind; but one has only to compare the effects of acetylcholine with succinylcholine, or *nor*-adrenaline with its methylated congener to realize how profound the effects of even slight changes of molecular configuration can be. The astonishing use which chemical evolution has made of the steroids is but another example of the same economy. It is likely that neurones possessing slight but definite differences in enzyme constitution may be differentially susceptible to neurohumoral agents. Such neurones may be unevenly distributed in topographically close, or widely separated areas in the central nervous system, these differences probably extending to the finest level of histological organization. Phylogenetically older parts, and perhaps, more particularly, the mid-line regions and the periventricular nuclei may, in terms of cell population and chemical constitution be significantly different from parts characteristic of late development.

As yet little information is available of the chemistry of the mosaic of cells, and cell groups making up the so-called reticular activating system. The neurones of this system, which is really a system of systems, bear a somewhat special and reciprocal relation to the afferent pathways which impinge upon them by way of collaterals. They are activated by these, but equally, through their activity, determine the ultimate perception of the signal arriving at the cortex by way of the sense-linked pathways (French, Verzeano and Magoun, 1953; Arduini and Arduini, 1954). The translation of afferent signals into perception may well depend on the

XUM

interaction of cortical and reticular elements, and may have its neural counterpart in the three dimensional apposition, and patterning of excitatory and inhibitory states in a very large cell population. The reticular formations are distinctive for the diffuseness of their connexions and of their effects. Equally, in this dense reticular field self-excitatory phenomena may predominate (Fessard, 1953), and the powerful operation of vectorial and spatial influences is likely. Slight variation in local titre of a neurohumoral agent in these key mid-line areas may thus profoundly affect the excitability of large neurone pools at a distance. It would perhaps be permissible to speak of the operation of chemical fields in these regions, which would depend on the rate of liberation, diffusion and destruction of locally produced neurohumoral agents. The agents in question may be either identical with or, more likely, derived from neuro-effector substances familiar to us at the periphery. Their number is probably small, but their influence upon integrative action of higher nervous activity may be profound. The basic states of consciousness may well be determined by variations in the local concentration of these agents.

The suggestion of the existence of three types of receptors within the brain must be regarded as but a first crude approximation in a study in which cytochemistry, pharmacology and electrophysiology are mutually complementary and interdependent. The recent refinement of cyto-chemical and microchemical techniques (Lowry *et al.*, 1954; Hydén, 1955; and Pope, 1955); of micro-electrode techniques within the central nervous system (Moruzzi, 1953); the development of methods for studying changes in local cerebral circulation (Kety, 1954); the growing number of data on the effects of punctate lesions, and of local electrical stimulation of selected areas on animal behaviour patterns; the ever-increasing range of natural and synthetic compounds exerting selective effects on higher mental function, form an inviting field for such combined studies. The pharmacology of behaviour must, of necessity, draw from each of these fields.

Advances in knowledge, though by no means solely dependent on methods are often inseparably linked with them; and present-day methods are well advanced.

## Summary

(1) The effect of various drugs on the electrical activity of the brain has been studied (*a*) in the conscious animal carrying permanently implanted electrodes, (*b*) in acute preparations sectioned at high spinal or mid-brain level (*encéphale and cerveau isolé* respectively), (*c*) in the barbitone anæsthetized preparation.

(2) The importance of studying the effects of drugs in conscious chronic preparations (in which changes in electrical activity can be observed simultaneously with behaviour) is emphasized.

(3) In the conscious animal, atropine and physostigmine caused a dissociation between electrical activity and behaviour. Atropine induced slow wave activity. This was similar to that seen in sleep; sleep, however, was never observed. Physostigmine led to an electrical pattern similar to that seen in the alert state, without a corresponding alerting of behaviour. The two drugs were mutually antagonistic.

(4) *l*-Hyoscyamine produced effects similar to those of atropine. *d*-Hyoscyamine and neostigmine were ineffective, except when the latter drug was given in high enough doses to induce peripheral symptoms.

(5) Amphetamine and LSD 25 in the conscious animal led to an alerting of the EEG, and behavioural excitement, there being, in the case of these two drugs, close correlation between electrical activity and behaviour. The effects of amphetamine were independent of the environment, and depended on dosage only. The effects of LSD 25 depended on factors in the environment, as well as upon the drug itself.

(6) In the acute preparations the effects of atropine were similar to those seen in the conscious animal, and were still present when either the upper spinal cord, or mid-brain were transected. Amphetamine caused alerting both of behaviour and electrical activity in the *encéphale isolé*, but had no effect on the *cerveau isolé*. LSD 25 had no effect on either of these preparations in the cat, but had some effect on the *encéphale isolé* preparation in the monkey.

(7) Atropine, physostigmine and LSD 25 modified the electrocortical patterns seen under barbitone anæsthesia. Amphetamine had no effect on barbitone induced activity. The depth of anæsthesia remained apparently unaffected by these drugs.

(8) None of the effects described could be correlated either with changes in respiration, or changes in systemic blood pressure.

(9) The grouping of the drugs in relation to their effects on electrical activity and on behaviour in the conscious animal, and the levels of section in acute experiment, is discussed. An attempt has been made to relate the findings to the known distribution of the reticular activating system, and the physiology of the brain-stem. It is suggested that three types of receptors are present in the brain. The receptors for LSD 25 may be specially related to the medial collaterals of the great afferent pathways.

(10) The possible operation of chemical fields within selected areas of the brain is discussed.

## REFERENCES

ADRIAN, E. D., and MATTHEWS, B. H. C. (1934) *J. Physiol.*, **81,** 440.
AMASSIAN, V. E. (1952) *Res. Publ. Ass. nerv. ment. Dis.* (1950), **30,** 371.
AMIN, A. H., CRAWFORD, T. B. B., and GADDUM, J. H. (1954) *J. Physiol.*, **126,** 596.
ARDUINI, A., and ARDUINI, M. G. (1954) *J. Pharmacol.*, **110,** 76.
BECKETT, S., and GELLHORN, E. (1948) *Amer. J. Physiol.*, **153,** 113.
BERGER, H. (1933) *Arch. Psychiat. Nervenkr.*, **101,** 452.
BONNET, V., and BREMER, F. (1937) *C.R. Soc. Biol., Paris*, **126,** 1271.

XUM

BONVALLET, M., DELL, P., and HIEBEL, G. (1954) *Electroenceph. clin. Neurophysiol.*, **6**, 119.
BRADLEY, P. B. (1952) Ph.D. Thesis, Birmingham University.
—— (1953) *Electroenceph. clin. Neurophysiol.*, Supplement III, 21.
——, ELKES, C., and ELKES, J. (1953) *J. Physiol.*, **121**, 50P.
——, and ELKES, J. (1953*a*) *J. Physiol.*, **120**, 13P.
——, —— (1953*b*) *J. Physiol.*, **120**, 14P.
——, —— (1953*c*) *Electroenceph. clin. Neurophysiol.*, **5**, 451.
——, and HANCE, A. J. (1956) *J. Physiol.* **132**, 50P.
BREMER, F. (1935) *C.R. Soc. Biol., Paris*, **118**, 1235.
—— (1936) *C.R. Soc. Biol., Paris*, **122**, 460.
——, and CHATONNET, J. (1949) *Arch. int. Physiol.*, **57**, 106.
BRENNER, C., and MERRITT, H. H. (1942) *Arch. Neurol. Pyschiat., Chicago*, **48**, 382.
CERLETTI, A., and ROTHLIN, E. (1955) *Nature, Lond.*, **176**, 785.
CHATFIELD, P. O., and DEMPSEY, E. W. (1942) *Amer. J. Physiol.*, **135**, 633.
COOKE, P. M., and SHERWOOD, S. L. (1954) *Electroenceph. clin. Neurophysiol.*, **6**, 425.
DELAY, J., LHERMITTE, F., VERDEAUX, G., and VERDEAUX, J. (1952) *Rev. neurol.*, **86**, 81.
ESSIG, C. F., ADKINS, F. J., and BARNARD, G. L. (1953) *Proc. Soc. exp. Biol., N.Y.*, **82**, 551.
FELDBERG, W. (1951) *Arch. int. Physiol.*, **59**, 544.
——, and SHERWOOD, S. L. (1953) *J. Physiol.*, **120**, 3P.
——, —— (1954) *J. Physiol.*, **123**, 148.
FESSARD, A. E. (1953) *In* Council for International Organizations of Medical Sciences. Brain Mechanisms and Consciousness, Oxford.
FORSTER, F. M. (1945) *Arch. Neurol. Psychiat., Chicago*, **54**, 391.
——, BORKOWSKI, W. J., and MCCARTER, R. H. (1946) *J. Neuropath.*, **5**, 364.
——, and MCCARTER, R. H. (1945) *Amer. J. Physiol.*, **144**, 168.
FREEDMAN, A. M., BALES, P. D., WILLIS, A., and HIMWICH, H. E. (1949) *Amer. J. Physiol.*, **156**, 117.
FRENCH, J. D., VERZEANO, M., and MAGOUN, H. W. (1953) *Arch. Neurol. Psychiat., Chicago*, **69**, 505.
FUNDERBURK, W. H., and CASE, T. J. (1951) *Electroenceph. clin. Neurophysiol.*, **3**, 213.
GADDUM, J. H. (1953) *J. Physiol.*, **121**, 15P.
GERARD, R. W., and LIBET, B. (1940) *Amer. J. Psychiat.*, **96**, 1125.
GIBBS, F. A., GIBBS, E. L., and LENNOX, W. G. (1937) *Arch. intern. Med.*, **60**, 154.
GRINKER, R. R., and SEROTA, H. (1938) *J. Neurophysiol.*, **1**, 573.
HAMPSON, J. L., ESSIG, C. F., MCCAULEY, A., and HIMWICH, H. E. (1950) *Electroenceph. clin. Neurophysiol.*, **2**, 41.
HESS, R., Jr., KOELLA, W. P., and AKERT, K. (1953) *Electroenceph. Clin. Neurophysiol.*, **5**, 75.
HIEBEL, G., BONVALLET, M., HUVÉ, P., and DELL, P. (1954) *Sem. Hôp. Paris*, **30**, 1880.
HYDE, J., BECKETT, S., and GELLHORN, E. (1949) *J. Neurophysiol.*, **12**, 17.
HYDÉN, H. (1955) *In* Waelsch's Biochemistry of the Developing Nervous System. New York, p. 358.
JASPER, H. H. (1953) *In* Council for International Organizations of Medical Sciences. Brain Mechanisms and Consciousness. Oxford.
KETY, S. S. (1954) Josiah Macy, Jr., Foundation. Trans. First Conference on Neuropharmacology. New York, p. 13.
LINDSLEY, D. B., BOWDEN, J. W., and MAGOUN, H. W. (1949) *Electroenceph. clin. Neurophysiol.*, **1**, 475.
——, SCHREINER, L. H., KNOWLES, W. B., and MAGOUN, H. W. (1950) *Electroenceph. clin. Neurophysiol.*, **2**, 483.

LOWRY, O. H., ROBERTS, N. R., WU, M. L., HIXON, W. S., and CRAWFORD, E. J. (1954) *J. biol. Chem.*, **207,** 19.
MILLER, F. R., STAVRAKY, G. W., and WOONTON, G. A. (1940) *J. Neurophysiol.*, **3,** 131.
MORUZZI, G. (1953) *In* Council for International Organizations of Medical Sciences. Brain Mechanisms and Consciousness. Oxford.
——, and MAGOUN, H. W. (1949) *Electroenceph. clin. Neurophysiol.*, **1,** 455.
POPE, A. (1955) *J. Neuropath.*, **14,** 39.
RHEINBERGER, M. B., and JASPER, H. H. (1937) *Amer. J. Physiol.*, **119,** 186.
RINALDI, F., and HIMWICH, H. E. (1955*a*) *Arch. Neurol. Psychiat., Chicago*, **73,** 387.
——, —— (1955*b*) *Arch. Neurol. Psychiat., Chicago*, **73,** 396.
SCHALLEK, W., and WALZ, D. (1953) *Proc. Soc. exp. Biol., N.Y.*, **82,** 715.
SCHWEITZER, A., STEDMAN, E., and WRIGHT, S. (1939) *J. Physiol.*, **96,** 302.
STARZL, T. E., and MAGOUN, H. W. (1951*a*) *J. Neurophysiol.*, **14,** 133.
——, TAYLOR, C. W., and MAGOUN, H. W. (1951*b*) *J. Neurophysiol.*, **14,** 479.
TOMAN, J. E. P., and DAVIS, J. P. (1949) *Pharmacol. Rev.*, **1,** 425.
TOWER, D. B., and ELLIOTT, K. A. C. (1952) *J. appl. Physiol.*, **4,** 669.
VOGT, M. (1954) *J. Physiol.*, **123,** 451.
WIKLER, A. (1952) *Proc. Soc. exp. Biol., N.Y.*, **79,** 261.
WOOLLEY, D. W., and SHAW, E. (1954) *Science*, **119,** 587.

# ON THE NATURE OF PAIN

BY

WILLIAM GOODDY

*From the National Hospital, Queen Square, London, W.C.*1

"*Le moment devoit fatalement arriver où, familiarisée avec cette confusion de la quantité avec la qualité et de la sensation avec l'excitation, la science chercherait à mesurer l'une comme elle mesure l'autre.*"

HENRI BERGSON. *Essai sur les données immédiates de la Conscience.* 1911.

"*Read not to contradict and confute, nor to believe and take for granted . . . but to weigh and consider.*"

FRANCIS BACON, 1620, *Novum Organum*

## INTRODUCTION

PAIN is one of the chief problems of Medicine. In a subject about which so much has been said in works of religion, philosophy, and the medical sciences and arts, the prospective student will be unable to make a complete survey; but those whose chosen duty it is to care for patients will agree that no aspect of pain should be outside their professional field. In this paper, an attempt is positively made to provide a reconstructive and synoptic " explanation " of pain, from the immense amount of analytical observations which the clinician may make for himself, or find in published work.

### (A) *Trends of scientific thought on the subject of pain and other sensations*

The neurological background to the subject may be studied in the reviews of Walshe (1942), Sinclair (1955), Weddell (1955), White and Sweet (1955) and Fischer-Williams (1956). The general literature shows a preoccupation with the peripheral features and factors. For example, the works of Head and Rivers (1908), Trotter and Davies (1909, 1913), Lewis (1942), Hardy, Wolff and Goodell (1952) and the numerous papers of Weddell and his associates have been concerned almost entirely with problems of cutaneous sensibility. Other types of pain have been less widely studied, and the problems of "central," "thalamic," and "cortical" pain have been regarded as on the fringe of neurology, in spite of the works of Dejerine and Roussy (1906), Head and Holmes (1911), Riddoch (1938) and Henson (1949). The group including "psychogenic" pain, the "functional" pains associated with depressive

psychosis, and hypochondria, is not commonly included in the neurological field at all.

It is here suggested that with the information available about the transmission of the nerve impulses, *after* such impulses have been started by a stimulus, "peripheral" or otherwise, it is possible and profitable to direct our attention to the processes of "feeling," and "perception," and the "effect" and "affect" of pain, not as a study separate from that of peripheral sensibility, but as a continuation upon neurological principles of the attempt to understand pain, and so to relieve it. Those complex problems, at present classified under "central pain," are beyond the realm of the physiologist, being impossible of solution by animal experiment. It is therefore especially important for neurologists to accept responsibility for directing research into such problems.

(B) *Theory*

In 1953, it was proposed in a paper on spatial orientation (Gooddy and Reinhold, 1953) that perception (defined as the qualitative experience of a conscious person, evoked by a series of events including the unconscious reception, selection, differentiation and integration of afferent stimuli) depends upon alterations in the strength and rate of impulses, derived from a peripheral organ and transmitted centrally. Emphasis was made upon the hypothesis that *there is a single process underlying all forms of sensation*, however diverse the various forms appear to the practical man. This single process was termed "motion sense" for the reason that afferent impulses, our sole means of making perceptual judgments, varied mostly in their *temporal* characteristics of rate and intensity, and little in their *spatial* (anatomical) distribution.

> ". . . all that the brain receives are the impulses in various quantities at various rates, occurring in what may be described as various temporal and spatial patterns."

Two points of especial relevance to the present theme were:

(i) the mediators (*patterns of impulses*) responsible for visual perception are no different in their physiologically demonstrated manifestations from those of pain perception. The nervous pathways and the activity mediated by them are qualitatively the same.

(ii) for the single final perception "I have felt a pin-prick," a succession of three distinct events is necessary, viz. a state of not feeling a prick, a state of feeling a prick, and a state of again not feeling a prick.

From these remarks there emerges the idea that we shall have in future to take notice of the temporal aspects of sensation to a far greater degree than is at present customary. The findings of anatomy on the one hand and of electrical recording on the other have given rise to many notions and statements which may eventually prove to have been misleading. Thus we read the words "pain fibres" or "localizable pain is associated with the

XUM

small medullate fibres of the B group" (Fulton, 1949) or, from the latest edition of a textbook of physiology (Evans, 1952):

> "The anterolateral columns (of the spinal cord) are concerned with pain, temperature and sex sensations, and unconscious afferents."

It is probable that the traditional theories of sensation are breaking down under the critical thought of contemporary investigators (Sinclair, 1955).

The problems of perception are investigated almost entirely at the periphery on the assumption that the appreciation of a pin-prick is a simple enough matter if there are suitable cutaneous receptors with centrally progressing connexions. Yet we have no knowledge at all of the position or arrangement of nerve impulses when the subject says "I feel a pin." The presumption that we see "*in*" the visual cortex or "*with*" it, or remember "*in*" the temporal lobe is fallacious. The fundamental importance of perceiving the errors inherent in the theory of cerebral representation with its baseless and obscuring implications, has been stressed by the writer (Gooddy, 1956).

If we reconsider the whole problem of sensation and perception in terms of impulse patterns (an idea of the greatest significance, probably first put forward by Nafe (1927, 1929)), and "motion sense," we see an alternative explanation for the many and diverse findings of experiment and clinical experience.

No single impulse or collection of impulses in a particular channel *is* a pain (or touch or visual) impulse. It is the combination of impulses in any number of anatomical (spatial) channels (fibres), of a particular rate of passage and frequency, which provides the basic "information," from which we believe perception is derived. This combination may be described (Gooddy and Reinhold, 1953) as a "dynamic pattern." The word "dynamic" has the implication of motive force associated with the passage of nervous energy.

The concept of a pattern of nervous activity is of immense complexity. Definition and clarification are essential, if this important concept is to assist and not hinder advancement. Young (1946) states:

> ". . . although this pattern (of activity within the central nervous system) above all others, lies at the centre of our existence and well-being, we are only just beginning to know anything about it."
>
> "But many, perhaps all, of the higher nervous centres are the seat of activity, occurring with a pattern in time and space, of which as yet we know hardly anything. . . . But physiology in general has not yet fully responded to the implications of the fact that there are continual and rhythmic changes of potential between neighbouring parts of the brain. I emphasize only one point, namely, that these changes are not dependent on external stimulation. . . . Knowledge of the existence of such intrinsic rhythms within the nervous system implies profound modification of our basic ideas about its functioning and it should help enormously in solving some of the most difficult problems in the physiology of sensation."

XUM

The word "pattern" implies some form recognizable by contrast with a background. It implies also a model or standard from which other models may be made or recognized by exact reproduction. In daily life a pattern is most commonly taken to mean some kind of design, imposed upon or built out of some solid material, such as paper, fabric of threads, plastic, stone or metal. Less commonly a pattern is recognizable, not from its spatial location, but by its temporal characteristics. The most familiar example, if not the most obvious, is in spoken and written language, music and dance. In these aspects of language and communication, it is the sequence of sounds, letters and movements that determines the pattern (e.g. *ate*, *eat*, *aet*, *tea*, *eta*). The musical tune affords the most easily understood example. In mentioning "codes," such as the Morse code, we find ourselves at the meeting-place with the language of the physiologist interpreting the activity of the nervous system. An example is taken from Eccles (1953):

> "All messages are conveyed in the form of a code, which is much simpler than the Morse code, in that it consists of only one uniform type of signal, the all-or-nothing nerve impulses, i.e. it is a code of dots only."

Though Katz (1952) gives reasons for believing that there are many modifying processes in the simpler notion of the all-or-nothing phenomenon, he too agrees that "conscious perception" is dependent on the medium of nerve impulses. His address is of great interest to neurologists, as this quotation shows:

> "Certainly, nothing in our conscious perception has not passed through the medium of nerve impulses, but equally certainly nothing in our consciousness bears any resemblance to nerve impulses, and to their discontinuous staccato nature. Nerve impulses are only carriers in the signals traffic, elements of a code, into which the message has been transcribed at the place of origin and from which it must be decoded at the other, receiving end."

A pattern, in this present paper, is used to call to the mind of the reader the idea of nerve impulses being in certain positions *in space and time:* in extension of this idea, the word "pattern" is defined as:

> "*. . . the space-time relationship of theoretically deducible and operationally detectible changes in the nervous system.*"

The idea of a spatial pattern is commonplace. The idea of a temporal pattern is less familiar to us though examples are not difficult to find. As might be expected, in temporal patterns there are essential spatial co-ordinates, and in spatial patterns there are temporal co-ordinates.

In the spatial pattern, the features of its composition appear together all at one time, and remain, in simple patterns such as those of embroidery or paintings, contemporaneously associated for the duration of the materials:

In a large design the pattern, apart from small motifs (each recognizable as a separate sub-unit or sub-pattern), is totally determined by the knowledge that if we alter our scale to include a larger area, we shall detect an integration of the sub-patterns into the total pattern. Often we employ the method of following (temporal) a thread or motif across or through a fabric or design, to tell from its subsequent appearance or repetition that it is an essential component of the total spatial pattern.

The temporal pattern (speech, music, dance) needs spatial co-ordinates for its localization and calibration. For example, the very rapid (accelerated) rotation of recorded tape reels causes the sounds of the voice to become unrecognizable, for reasons of pitch (even though the ratio of the different pitches of the verbal sounds is preserved). The written word needs the spatial conventions of its particular civilization; e.g. Eastern nations using a right-to-left progression or even a vertical progression. In music, the tune is associated with spatial positions, not only on the keyboard, tubes, strings of the instruments, but also on the notational frameworks of the musical page, with its complex collections of clefs, ledger lines, and signs for "sharp" and "flat" notes.

(C) *Semantics of Pain*

Brain (1955) has pointed out the importance of neurological semantics:

> "The relationship between brain mechanisms and consciousness is not purely a semantic question, but semantics play so large a part in it that no writer who fails to recognize this is likely to get very far."

Pain is a feeling or sensation or perception, which, though producible by many different causes, is recognized by man from its *quality*. Whatever the cause of pain, be it a burn or bereavement, we are certain of the experience as a painful one; yet we are incapable of exact description of pain, and the whole structure of language contains not a single method of quantitative analysis. This thought is expressed by Virginia Woolf in an essay "*On being ill*" :

> "English, which can express the thoughts of Hamlet and the tragedy of Lear has no words for the shiver and the headache. It has all grown one way. The merest schoolgirl, when she falls in love, has Shakespeare or Keats to speak her mind for her; but let a sufferer try to describe a pain in his head to a doctor and language at once runs dry."

Pain is never described in units of length or breadth or weight or size. At best we fall back on analogy of a conventional type, which is usually elaborately and admittedly inaccurate. Eventually we are forced to call to the *mind* of another person the experiences he may have had in similar

circumstances; or we make the suggestion which at the outset is known to be false, that our feeling is such as might be experienced by someone undergoing a certain procedure. So the word "toothache" becomes a code abbreviation for the whole experience of one sufferer, to be contrasted with the possible recent or remote, or even theoretical or imaginary experience of the observer; or we say "pins and needles," knowing that the common experience so described does not resemble the actual sensation provided by multiple and successive applications of "real" pins and needles. "Burning" and "tearing" pains are manifestly unlike the feelings of being burnt or torn.

A pain is always *pain*, a quality like goodness, or justice. Therefore *there can be no pathways nor nerve-endings for pain.* Walshe (1942) has said:

> "In short, the notion of pathways for localization or for discrimination, is in the same category as that of pathways for truth or beauty, and is but a figment of the observer's mind."

The notion of pathways for pain is also but a figment of the observer's mind.

The most useful auxiliary information in assessing pain is obtained from the history of the qualities of the pain. It is possible by comparing a measured estimate of the temporal features of a pain with the known patterns of pains associated with different categories of disease sometimes to make deductions about the underlying cause. A pain lasts so long, a week or a day or a second. It recurs every so often. It ceases for certain periods. There may be a causal relationship to events in the history of a pain. There is sometimes, at a particular moment, an obvious cause, such as trauma. There may be a temporal relationship to methods of treatment, such as analgesic drug administration, rest, or the realignment of broken bones. We are now at the point of being forced to ask the question so commonly avoided "How does the detection of the abnormal pattern give rise to pain?"; and the second question "Where does the neurophysiological state break through to 'feeling' and psychological states?"

This insoluble problem is not a valid one. The confusion has arisen from the error of changing from one semantic channel to another. The two channels in question are, respectively, *quantitative* and *qualitative*. Both aspects of reality, quality and quantity, have their proper place in human affairs. They are also both "psychological," for even *the most factual mathematical, statistical, experimental results devised in the mind of the scientist are referred mentally by him to their relation in his life.* No theory of semantics can provide a cross-channel from quantity to quality, as the scientist falsely suggests in his desire for a simple connexion between mind and brain. As Brain points out (1955) in reviewing the symposium "Brain Mechanisms and Consciousness" (1954):

XUM

> "From the semantic standpoint this might be called a symposium upon a hyphen, the hyphen in the brain-mind relationship."

This hyphen, by its very appearance, implies a physical link between brain and mind, and as currently used in neurology has lost its correct meaning of associating two *ideas*. The word "mind" means something by definition not located in space. The word "brain" means the material object inside the head. There can be no link between the two, for they are in different categories of language. For analogous example, velvet is smooth. If velvet is damaged its smoothness is impaired. But one cannot go from a piece of velvet to a piece of smoothness, as one can go to a piece of silk.

Again we find the semantic error. In the attempt to keep a working hypothesis in spite of its manifest absurdity, the scientist sets himself further tasks which are also incapable of solution. We have only to consider the phrase "physical treatment of mental disease" to see the error. In these methods, physical alterations are made in the nervous system, but cannot possibly be made physically in the mind. We are then forced to make the deduction that the local "physical" pain associated with mental illness is the symptom of abnormal functioning of nervous tissues in the cerebral cortex as pain in a finger is the symptom of abnormal functioning of the peripheral tissues.

Finally, let the scientist ask himself "How heavy, how long, how many miles per hour is pain, how many right angles are there in a bruise, how high is colic?" He will see how there can be no answer to his questions, for language is not constructed to provide one. He will then see that there are no pain impulses in the peripheral nerves, not any red or green visions in the optic system.

It is now proposed to use the foregoing theoretical considerations to illustrate the following ideas:

(i) *that the feature common to all types of pain is the unusual nature of the cause.*

(ii) *that such a cause produces unusual patterns in the nervous system.*

(D) *Clinical classification of causes of pain*

(1) "*Peripheral*" *group*

The nature of *peripheral causes* of pain is extremely diverse. There are the following (arbitrary) categories:

(*a*) *punctures of superficial and deep tissues* (*wounds*)

(*b*) *loss of surface tissues* (*abrasions, ulcers*)

(*c*) *damage by disease or injury to deep structures, such as joints, serous membranes, meninges,* (*malignancy, inflammation, trauma*)

(*d*) *exposure to temperature not habitually experienced* (*freezing, burning, scalding*)

(*e*) *alterations of tissue tensions*
  (i) fluid changes—swelling, bruising, blisters, injections
  (ii) traction—visceral interference
  (iii) distension by fluid or gas, in viscera—retention, or cerebral ventricles—hydrocephalus, encephalography
(*f*) *unnatural muscular activity* (*cramp, colic, spasm, convulsion*)
(*g*) *conditions of vascular inadequacy or disease* (*angina, claudication, migraine, inflammation*)
(*h*) *extremes of normal stimulation* (*odour, light, sound, vibration, tickle*

All these are well recognized and find some form of expression in common language by the whole human race with but few exceptions (Jewesbury, 1951). The second group in order of central (towards the brain) progression is formed by the conditions admirably described by Riddoch (1938) in the Lumleian Lectures of the Royal College of Physicians of London. In spite of their clinical importance and theoretical significance, these types of pain are little known and rarely considered by the majority of medical scientists and philosophers. These pains are seen in association with lesions *central* to the supposed site of "pain endings," *that is, the lesions lie in the anatomical substance of the nervous system itself.* They may be noted as follows:

(2) "*Central*" *group*

(*a*) lesions of peripheral nerves (trauma, neuritis)
(*b*) lesions of the posterior nerve roots (compression, tabes dorsalis)
(*c*) lesions of the spinal cord (tumours, cavities as occur in syringo- and hydromyelia, inflammation (myelitis), demyelinating disease such as disseminated sclerosis and neuromyelitis optica, vascular lesions)
(*d*) lesions of the brain-stem (tumours, vascular lesions, syringo-bulbia)
(*e*) lesions of the central cerebral structures, especially the thalamus (tumours, vascular lesions)
(*f*) lesions of the basal ganglia, causing dystonia
(*g*) (possibly) lesions of the cerebral cortex (causing, by production of disordered movement, pain in the limbs)

(3) "*Psychological*" *group*

Thirdly, there is an important group comprising the so-called "psychological," or "mental" pains. This group is commonly divided into "functional disorders," anxiety states, depression with physical symptoms,



XUM

and hypochondria. It is often an additional diagnostic label to an established physical condition such as peptic ulcer, colitis, hypertension, or psychiatric diseases such as schizophrenia. Disorders in this group are sometimes amenable to physical methods of treatment, such as electroconvulsive therapy, insulin coma, and occasionally, leucotomy. The physiological basis of such disorders and the principles underlying their treatment has been formulated by Gellhorn (1953).

(E) *Clinical Physiology and the pattern theory*

If we follow the idea of the pattern of nervous activity as the determining factor in the production of sensation (comfort when the patterns are caused by familiar external agents or by skilled movements: discomfort when they are altered from the normal) we see that the nervous system constantly is presenting, from one part to another, its patterns from which there is no escape in human behaviour but unconsciousness. Even in sleep the process continues, though the bulk of dreams is probably not produced by peripheral stimuli, but by central activity uninfluenced by the additional components provided by the waking state. Central lesions are well known to produce hallucinations, and may be due to tumours, trauma, drugs, metabolic disturbances, and perhaps schizophrenia.

If we assume that on emerging from infancy, at that time when "memory becomes continuous," we accustom ourselves to the patterns occurring at all times, we find some explanation and justification for the need of protection of the young and the processes of learning those self-preservative skills, both practical and social, which enable us to survive physically and mentally in spite of many natural hazards. "Once bitten, twice shy" is the complete expression of all that neurophysiology and experimental psychology tell us. It is easy to recall the painful effects of inexperience, especially those of childhood, with its cuts, burns, falls, bruises and colic. Such accidents are rare in adult life only because of our skill in avoiding them. We prevent ourselves creating in our nervous systems the patterns of impulses which will "upset us." With experience it is even possible to injure oneself, by a blow followed by acute swelling, and know the pain about to occur before the physiological mechanisms have provided its basis. We may avoid painful situations, such as dental procedures, by hallucinations of previous pain revived from memory, which cause us to delay a visit to the dentist. Similarly we may seek some slight pain, in order that worse may be avoided.

It was stated above that in all the forms of pain production, so diverse in character, the sole common factor is the unusual nature of the provocation, which itself must be responsible for unusual patterns of nervous activity. For example, with a burn, a patch of skin is altered in structure in a number of ways, and nerve fibres are set into activity in numbers

and combinations which are never found when the patch of skin is normal. Pain arises as soon as the altered state occurs, and is often decreased by simple remedies which have the effect of restoring the injured part to a condition like the normal. Various methods of "protecting it from the air" are effective. Oily applications, or tanning agents, providing an artificial skin, are well known for their pain-relieving properties, so much so that they may be employed in disregard of the current theories of burn management. Painful movements, a quite different problem, are treated by rest and immobilization.

Accepting the notion of pain being associated with unusual patterns in the nervous system, there is implicit the non-specificity of sensations, that is, *all sensations have but a single and common substrate, the pattern.* This pattern is not that of one impulse in one pathway, but the grouping of a number, from various channels. We may have been misled by the interpretations of the experimental work of Gasser (1935) and Erlanger and Gasser (1937), for these authors, after noting the conduction rates of fibres of various sizes (in a nervous channel), decided that those of a certain size were the pain fibres, because only when those fibres were conducting did pain arise. It is more reasonable to suppose that pain arises when factors additional to those of the non-painful state are added to that usual pattern: for sensations cannot reside in nervous tissue.

As recently as 1942 Lewis constructed a theoretical system of a pain-producing substance and a special "nocifensor" nervous apparatus, to substantiate his notions of a peripheral pain system. Kelly (1955) in a brief but compelling article points out that Lewis's factor P cannot be detected in the peripheral blood, and that it is partial nerve block and not the ischæmia of muscles which is the cause of pain arising in muscle acting in the abnormal (unusual) circumstances produced by placing a cuff round the limb (constricting both nerves and blood vessels). Nathan (1953) has shown that painless lesions in skin and muscle become painful when the limb is constricted, and also when only the efferent nerve is compressed. When the painless lesions change to painful ones, on limb constriction, the nerve concerned is found to be conducting more impulses than formerly. Kugelberg (1946) also has shown that there is an intensified electric discharge from a compressed nerve. Finally, muscles in the compressed limb become weak even if not exercised (Marshall *et al.*, 1954) and the deep reflexes disappear (Gellhorn and Thompson, 1944).

There is, therefore, from simple clinical study and from "clinical science," adequate evidence that the theory of pain and patterns is reasonable.

We find that disordered patterns (rate, amplitude, time and space) are the most obvious neurophysiological and anatomical accompaniments on pain. The "motion sense" (Gooddy and Reinhold, 1953) is the

XUM

detection of abnormality as common denominator; that is, the contrast with normal, (usual, habitual) and currently existing sets of patterns.

(F) *The relation of physical pain to "psychogenic" pain*

At present, pain is often classified on anatomical grounds, and we take for granted the validity of pains peripherally produced (such as burns, cuts, sprains, externally; and visceral pain from internal structures, such as joint linings, serous membranes and viscera). We are satisfied also with pain originating in the central nervous system itself, at levels anatomically lower than the cerebral cortex (as in disseminated sclerosis, syringomyelia and syringobulbia, vascular and neoplastic lesions of the brain stem and thalamus). We must then ask why, if the cerebral hemispheres themselves are composed of nervous tissue of similar pattern to the rest of the nervous system (connected neurones) there is no pain appropriate to their dysfunction.

It is here suggested that the type of pain specific to the cerebral hemispheres above the thalamus is a physical one, at present wrongly labelled psychogenic. If this theory is correct, there is no difficulty in understanding why such disorders as depression, and agitation, and their "associated physical symptoms", should respond to physical methods of treatment.

(G) *Unitary system of pain*

(i) The first theoretical implication of the foregoing pages is that any nervous pathways are potential "pain pathways" ; that is, any pathway may be the one that provides the nervous circulation (Gooddy, 1949, 1956) with the impulse patterns that are associated with the perception of pain. All that is necessary for the production of pain is the existence, in any nervous tissues, of the special impulse combinations (patterns) which, as they circulate,[1] provide a sufficient degree of variation from the patterns circulating when he is not in pain. This idea was well expressed by William James (1905):

> "It is certain that sensations of every order which in moderate degree are rather pleasant than otherwise, become unpleasant when their intensity grows strong."

We find here the reason for the well-known intractability of "central pain." In the cases of painful stumps, it is often found that the usual surgical procedures are effective only for short periods. In the treatment of such cases it is customary to start at the periphery and carry out excisions of neuromas and any other tissues which show signs of damage. Within a few months pain is once more noticeable, and soon works up to its former intractable degree. Peripheral nerves may be blocked or severed, again with only temporary relief. On further recurrence of pain, the posterior roots of the spinal cord may be cut. Later, antero-lateral

[1]The idea of the circulation of the nerve impulse is the subject of a separate paper.

cordotomy is carried out. Later still, thalamic coagulation may be tried; then cortical topectomy; and at last leucotomy. After all these severe measures, the pain may still return. When the physician and surgeon confess themselves helpless, the patient may commit suicide. This desperate series of events suggests one process only: that *unless the whole nervous system is destroyed, the abnormal patterns gradually establish themselves anew, in one set of channels after, as the former channels are denied them.*

The impulses re-route themselves, and in a few months have gained sufficient strength (stand out in contrast with the background of nervous activity) to re-create the circulation of abnormal patterns. If the natural (most direct) channels are interrupted by surgery, it is likely that indirect channels including those of the sympathetic nervous system will be used. It is well known that sympathectomy is sometimes effective in the relief of pain. Such success is likely to depend on the route of the impulses from the affected parts.

(ii) *The second theoretical implication* is that alteration of the impulse patterns, when pain is present, should result in alteration in the quality of the pain. This suggestion is exactly exemplified in the effect on pain of such diverse agents as nerve section and block, drugs, hammering and drugs. It is noteworthy that repeated nerve block by peripheral injections of local anaesthetic agents is one of the most effective forms of treatment of intractable pain, even after more fundamental procedures have been tried unsuccessfully.

(iii) *The third implication* is that pain of moderate severity but great persistency may become pleasurable. In the end, the patterns at first contrasting with the ones to which the patient is accustomed become those to which he has adjusted and so comes to recognize as the usual and therefore preferable ones. Some patients, if relieved of chronic pain about which they formerly much complained, find they have lost something valuable and essential; and are ungrateful for the relief medically provided. (Penman, 1954.) Some pains become pleasurable only after practice, as in the enjoyment of bitter or burning drinks, smoking, or extremes of physical exertion.

Contrariwise, pain may result from prolonged pleasure, especially if satisfied without stint (revulsion). It is possible that the whole problem of addiction is derived from an unbalanced cycle of satisfaction-pleasure and withdrawal-pain.

On occasion it may be difficult to decide if a sensation is pleasant or painful; and especially at what point a sensation of increasing intensity changes from pleasant to unpleasant (warmth-burning).

(iv) *The fourth implication* is that by concentrating on the unitary theory, as outlined above, of a single process underlying the varied manifestations of pain, the clinical worker may be able to treat those patients

XUM

whose cases are marked by severe pain, in a more comprehending and comprehensive manner. It should be possible (i) to make more accurate judgments of the likely course of painful symptoms: (ii) to plan preventive measures: (iii) to assist the immediate symptoms by measures both local *and general*: (iv) to devise new methods of treatment of pain, not empirically, but with deliberate planning towards control of the patterns of nervous activity: (v) to avoid those misjudgments of the degrees of alleged "mental" aggravation of "physical" symptoms, which often add greatly to the patient's suffering.

I wish to express my gratitude to Dr. Margaret Reinhold, who has greatly assisted me with constructive criticism and advice. I am indebted to Dr. Peter Nathan for the quotation from Virginia Woolf.

## REFERENCES

BRAIN, W. R. (1955) *Brain*, **78,** 669.

Council for International Organizations of Medical Sciences (1954) Brain Mechanisms and Consciousness. A Symposium. Oxford.

DEJERINE, J., and ROUSSY, G. (1906) *Rev. neurol.*, **14,** 521.

DUNNE, J. W. (1948) The Serial Universe. London.

ECCLES, J. C. (1953) The Neurophysiological Basis of Mind. Oxford.

ERLANGER, J., and GASSER, H. S. (1937) Electrical Signs of Nervous Activity. Philadelphia.

EVANS, C. L. (1952) Starling's Principles of Human Physiology, 11th Ed. London.

FISCHER-WILLIAMS, M. (1956) *Brit. Med. J.*, **1,** 533.

FULTON, J. F. (1949) Physiology of the Nervous System, 3rd Ed. New York.

GASSER, H. S. (1935) *Proc. Ass. Res. nerv. Dis., Baltimore* (1934) **15,** 35.

GELLHORN, E. (1953) *Physiological Foundations of Neurology and Psychiatry. Minneapolis.*

——, and THOMPSON, L. (1944) *Proc. Soc. exp. Biol., N.Y.*, **56,** 209.

GOODDY, W. (1949) *Brain*, **73,** 312.

—— (1956) *Brain*, **79,** 167.

——, and REINHOLD, M. (1953) *Brain*, **76,** 337.

HARDY, J. D., WOLFF, H. G., and GOODELL, H. (1952) Pain Sensations and Reactions. Baltimore.

HEAD, H., and HOLMES, G. (1911) *Brain*, **34,** 102.

HENSON, R. A. (1949) *Brain*, **72,** 576.

JAMES, W. (1905) Textbook of Psychology. London.

JEWESBURY, E. C. O. (1951) *Brain*, **74,** 336.

KATZ, B. (1952) Different Forms of Signalling employed by the Nervous System. London.

KELLY, M. (1955) *Lancet*, **1,** 747.

KUGELBERG, E. (1946) *Brain*, **69,** 310.

LEWIS, T. (1942) *Pain. New York.*

MARSHALL, J., POOLE, E. W., and REYNARD, W. A. (1954) *Lancet*, **1,** 1151.

XUM

NAFE, J. P. (1927) *Amer. J. Psychol.*, **39,** 367.
—— (1929) *J. gen. Psychol.*, **2,** 199.
NATHAN, P. W. (1953) *J. Neurol. Neurosurg. Psychiat.*, **16,** 144.
PENMAN, J. (1954) *Lancet*, **1,** 633.
RIDDOCH, G. (1938) *Lancet*, **1,** 1093, 1150 and 1205.
RIVERS, W. H., and HEAD, H. (1908) *Brain*, **31,** 323.
SINCLAIR, D. C. (1955) *Brain*, **78,** 584.
TROTTER, W., and DAVIES, H. M. (1909) *J. Physiol.*, **38,** 134.
——, —— (1913) *J. Psychol. Neurol., Lpz.*, **20,** Ergänzungsheft, p. 102.
WALSHE, F. M. R. (1942) *Brain*, **65,** 48.
WEDDELL, G. (1955) *Annu. Rev. Psychol.*, **6,** 119.
WHITE, J. C., and SWEET, W. H. (1955) Pain. Its Mechanisms and Neurosurgical Control. Springfield, Ill.
YOUNG, J. Z. (1946) Patterns of Substance and Activity in the Nervous System. London.

# NOTICES OF RECENT PUBLICATIONS

## A TRIBUTE TO SIR GORDON HOLMES

*Selected Papers of Sir Gordon Holmes.* Compiled and Edited by F. M. R. WALSHE. 1956. Pp. 262. Figs. 85. MacMillan & Co., Ltd. Price 20s. net.

In the compilation of this volume Sir Francis Walshe must have found the task of selection a hard one. Many of its readers will regret the omission of papers which they would especially wish to possess on account of their value and relative inaccessibility, as, for example, some of those dealing with ocular movements. But as a tribute to the achievements of Sir Gordon Holmes it is fitting that papers should have been chosen as examples of his work on three subjects which he made especially his own: the cerebellum, the cortical representation of vision, and visual orientation and attention.

The first paper of the series on the cerebellum, written in collaboration with Grainger Stewart, is, apart from its intrinsic value, of historical interest, for it is dedicated to Edinger, under whom Holmes served a full apprenticeship in the methods of the laboratory, which doubtless contributed to the minute observation, detailed analysis, and careful reasoning of all his subsequent work. The most important of the cerebellar papers is the series of three Croonian Lectures on the Clinical Symptoms of Cerebellar Disease and Their Interpretation given in 1922, to which is appended the Hughlings Jackson Lecture of 1939 on the same subject. The Croonian Lectures are classics, which every neurologist must have read with admiration of the author's powers of observation, and ability to translate what is seen at the bedside into physiological terms. Holmes's demonstration of hypotonia in cerebellar lesions was for long questioned by the physiologists, who had been unable to produce this symptom by ablation in animals, but the correctness of his observation was confirmed when these experiments were extended to primates.

Physiologists since 1939 have made discoveries which oppose some of his conclusions. He found no evidence to suggest that the cerebellum was an organ for equilibrium, considering the disorder of balance in cerebellar disease to be secondary to disorder of movement, whereas it is now accepted that ablation of the flocculo-nodular lobe in animals results in a pure disorder of equilibrium. The function of the anterior lobe in inhibiting muscular contraction was also unknown at the time of Holmes's work. In the paper with Grainger Stewart on Cerebellar Tumours enhanced tonic activity from a destructive lesion is described but interpreted as an irritation phenomenon. Nevertheless unilateral ablation of the neo-cerebellum in the chimpanzee has been shown to produce symptoms which in every particular resemble those described by Holmes in man, and his analysis of the factors contributing to the disorder of movement has been appraised by Fulton as "immediately

applicable to the neo-cerebellar syndrome as seen in the higher primates." Clinical observation had here anticipated physiological experiment. What is chiefly remarkable in these papers on the cerebellum is the scientific approach to clinical problems. Where most clinicians would have been content with the demonstration of signs adequate for practical purposes of diagnosis, Holmes extracted all he could out of every case for the advancement of physiological knowledge.

Concerning the papers on the Cortical Representation of Vision there is nothing to add to the editorial note of introduction. Before the publication of this series of observations the point-to-point representation of the retina in the occipital cortex was not generally agreed or fully known. These papers give the now generally accepted conclusions on this matter.

The two papers on disturbance of visual orientation are especially welcome since neither appeared in BRAIN. The first presents six cases examined in every detail, each observation leading to a further question to be answered by yet another method of observation. The value of these studies in the field of the disorders of perception, both for their intrinsic merit and as a model for further investigators, is unsurpassed. One of his observations was that in all these cases stereoscopic vision was preserved. In the last paper of the series a case is described in which spatial disorientation was associated with loss of stereoscopic vision, and there was also loss of visual memory.

Appended to the volume is a bibliography of published work of Sir Gordon Holmes which will be invaluable. For those who have had the fortune to be taught by Holmes at the bedside the re-perusal of these papers will evoke memories rich in admiration, affection and respect, and all students of neurology will be grateful for a volume on their shelves which gives ready access to a series of studies by an unrivalled master of his craft.

C. P. SYMONDS.

## PARKINSON AND PARKINSONISM

*James Parkinson*, 1755–1824. A bicentenary volume, edited by MACDONALD CRITCHLEY, with the collaboration of WILLIAM H. MCMENEMEY, FRANCIS M. R. WALSHE and J. GODWIN GREENFIELD. 1955. Pp. 268. Figs. 11. London: Macmillan & Co., Ltd. Price 15s. net.

The primary purpose of this book, sponsored by the guarantors of BRAIN, is to reprint James Parkinson's famous Essay on the Shaking Palsy, on the occasion of the bicentenary of the author's birth. The essay is preceded by a long and informative biographical essay on the author by Dr. W. H. McMenemey, and it is followed by two essays on Parkinson's disease—one on the pathology, by Dr. J. G. Greenfield, and the second, presenting an analysis of the clinical syndrome by Sir Francis Walshe. As there is also an introductory essay by Dr. Macdonald Critchley the book consists in all of five essays relating to James Parkinson and his disease.

While much has been added to Parkinson's original description of the clinical syndrome, it is remarkable that after one hundred and forty years the essential pathology of paralysis agitans still eludes us. One of Parkinson's

XUM

declared objects in publishing his essay was "the leading of the attention of those who humanely employ anatomical examination in detecting the causes and nature of diseases, particularly to this malady. By their benevolent labours its real nature may be ascertained, and appropriate modes of relief, or even of cure, pointed out." This hope remains unfulfilled. Dr. Greenfield's essay is largely historical, but his survey shows paralysis agitans in its classical form "to be a systemic degeneration of a special type, affecting a neuronal system whose nodal point is the substantia nigra." The monograph of Foix and Nicolesco, which emphasised, and illustrated so beautifully, the degeneration of the pigmented cells in the various structures throughout the brain-stem was perhaps before its time, and the selective degeneration suggests to us now that we may be dealing with a metabolic disorder, or, in Dr. Greenfield's words, "a problem whose solution may be found in enzyme chemistry, or some other new field of investigation."

*The Neurosurgical Alleviation of Parkinsonism.* By IRVING S. COOPER, M.D., Ph.D., F.A.C.S. 1956. Pp. 104. Figs. 68. Published by Charles C. Thomas, Springfield, Illinois. Price £3 3s. 0d.

The surgical technical aspect of this book, important though it may be, is of much less importance than the general problem of the alleviation of Parkinsonism by surgical means, and the physiological questions which it raises. The author has had success—apparently striking success—with two surgical methods of treatment, both of which are aimed at destruction of the globus pallidus or its efferent fibres.

The anterior choroidal artery provides the principal blood supply to this nucleus, and although it is known that the softening which results from its occlusion is somewhat variable in its extent and distribution, nevertheless great alleviation of rigidity and tremor has been obtained in consequence of its occlusion by surgical means; the results are classified as "good" in 65 per cent of 50 cases. The other method consists of placing a lesion, by means of apparatus which the author has devised, in the most medial and lower portion of the globus pallidus; the lesion is produced by injection of a small amount of absolute alcohol after a favourable effect has been obtained by injection of "Procaine" (American terminology). Reference is made to the similar work of Fénélon and of Guiot. After seventy operations it is estimated that there is practically complete alleviation of rigidity in 80 per cent of properly selected cases, and complete alleviation of tremor in 60 per cent.

While there is little reason to doubt that these effects result from destruction of the medial portion of the globus pallidus (or its efferent fibres) hardly any pathological control evidence is presented.

The experimental work of Whittier, Carpenter and Mettler led to the conclusion that there was a continuous outflow of impulses to the motor system from the globus pallidus, and that when the corpus Luysii was destroyed, these impulses became completely irregular, and hemichorea (hemiballismus) resulted. However, the globus pallidus has many afferent connections, and impairment of some other parts of its controlling system may well lead to tremor and to rigidity. (The physiological relationship between these two is still obscure.)

XUM

Alternatively, or in addition, degenerative changes in the globus pallidus itself may lead to irregularities in its function.

From the practical aspect, the position is that, whatever the pathogenesis of parkinsonian tremor and rigidity, they probably depend on the outflow from the globus pallidus, and that operations are now being practised which seem capable of interrupting this outflow and so abolishing these symptoms without producing other disabilities. The treatment is, of course, still in the experimental stage and has been applied only to the alleviation of severe cases. It seems permissible to hope that, once the outflow from the globus pallidus has been interrupted, anatomical extension of the primary degenerative condition need not lead to the renewed appearance of symptoms—in other words the effects of the operations may be permanent in spite of progress of the disease.

This book is an important contribution to its subject.

J. PURDON MARTIN.

## ELECTRO-ENCEPHALOGRAPHY

*Systématique et Électroencéphalographie des Encéphalites et Encéphalopathies.* By J. RADERMECKER. Pp. 244. Figs. 78. Institut Bunge, Antwerp. Masson. Paris. Price 2,800 fr.

This monograph is the fifth supplement to the journal of electro-encephalography and clinical neurophysiology, but it is the first to appear in monograph form, its predecessors having been symposia. It has the same format as the journal.

Dr. Radermecker has made a survey of much of what is known of the clinical, pathological and electro-encephalographic features of the encephalopathies, whether infective or toxic and he has reviewed the literature assiduously. What seems so surprising is that Dr. Radermecker's descriptions, classifications and conclusions in such an amorphous subject are so obviously acceptable. We might expect much more dispute where so little is known, where symptomatology is so variable, and where divisions are so indistinct. Closer study shows that agreement is really in observation, and that apart from known causal correlates such as the pattern of disturbance associated with the special fevers, meaningful relationships have hardly begun to exist in the encephalopathies. Clinical syndromes overlap, and tissue reactions are similar, the distribution of lesions is ubiquitous, the virologists often fail to identify an organism and the electro-encephalogram may help little.

Yet this monograph presents what is known lucidly, and it is based on very detailed histopathology, beautifully presented and related to commonsense clinical classifications. That is its contribution, and the large line-drawings of serial slices of the neuraxis showing the site of lesions in different forms of encephalitis are a valuable summary of Dr. Radermecker's evidence. The electro-encephalographic changes on the other hand have the unique value of being serial in time, and in presenting a dynamic feature of disorders in which nearly every other observation is negative, and yet so far they do not help us much. There are the periodic electrical changes seen in subacute

XUM

inclusion-body encephalitis, and there are the reflections in hemisphere recording of mesencephalic disturbances. Throughout—in behaviour, electroencephalography, and histology—the weight of the effect of these disorders is seen to be upon the midbrain and basal structures, and it is because of this that they so greatly interest workers in clinical electrophysiological laboratories.

DENIS WILLIAMS.

## CLINICAL NEUROLOGY

*Progress in Neurology and Psychiatry. Annual Review. Vol. X.* By E. A. SPIEGEL. 1955. Pp. 645. New York: Grune & Stratton. £3 10s. 0d.

This is the tenth of the annual series of volumes in which a large group of contributors review the literature of the preceding year in their own particular field of the nervous system. The object is to bring the reader up to date in the fields of neurology, psychiatry and neuro-surgery, and the basic sciences. Like all books of this kind there is inevitably considerable variation in the manner of presentation and the value of the material presented. Each chapter is a synopsis of papers that have caught each individual author's eye, and on the whole, the ground appears to have been covered fairly fully. Of particular interest is the chapter on the surgical treatment of pain and motor disorders and also those operations that are covered by the dreadful term "psychosurgery." It is apparent from the spate of papers covered on these subjects that much yet remains to be learnt in this fascinating field and that much confusion has arisen on account of the almost universal tendency to rush into print after unscientific selection of material and an insufficiently detached appraisal of results on too few patients. There is an excellent bibliography at the end of each chapter which is in itself extremely valuable.

There is a place for this sort of book, for the volume of publications is now so great that no single person could hope to keep abreast of the literature throughout his subject. Over 6,000 papers are referred to in the text, and this is a review of one year's literature only. It might be said therefore that it is as a reader's guide that this sort of book finds its niche. It is an indication of the papers to be read rather than a substitute for reading them, as the matter is perforce too concentrated to be of much value other than as a guide. One must be grateful to the various authors for their industry in publishing this annual review.

*Clinical Studies in Neurology.* By HARRY LEE PARKER. 1956. Pp. 364. U.S.A.: Charles C. Thomas. Price 47s. 6d.

In 1934 the author was invited to take the chair of neurology at his parent university, Trinity College, Dublin, and he was elected senior staff physician at the Richmond Hospital. While there he instituted a series of Tuesday morning lecture demonstrations, and this book presents each of these apparently as they were given.

Dr. Lee Parker's personality becomes evident as one reads. It is obvious that he is a genial, kindly person with a great interest in his patients

XUM

and his subject—quite definitely what would be described as a personality, and therefore certainly a good teacher. It is easy to imagine that those attending the demonstrations would not fail to leave with something new learned. Nevertheless it is difficult to see what exactly the purpose of this book is and to whom it is directed. The reviewer enjoyed reading it, and it is clear that the author enjoyed writing it, but it could better be classified as a pleasant Saturday afternoon's reading, rather than a serious textbook.

The lecture-demonstration has a traditional and extremely valuable part to play in presenting neurological disorders to what Dr. Lee-Parker would call the neophytes, but in the reviewer's opinion it is essential that a clinical demonstration should be spontaneous and unrehearsed and, equally important, that there should be a responsive audience. If it is rehearsed, it tends to degenerate into a formal lecture. The latter should surely encompass the whole story, but a clinical demonstration fails if it attempts to be an exhaustive treatise on disease. For this reason the impact of the clinical demonstration is lost completely in attempting to put them in book form. What may well be effective theatre and vigorous teaching on the best type of patient—that is, the one who co-operates to the full in the theatre—and with an audience reacting to the occasion, sounds too often like a tedious striving after effect when presented in black and white and read in cold blood. Who has not experienced the embarrassment of blank looks when trying to recapture in descriptive phrases the antics of the comedian who, the night before, brought the house down. It seems, therefore, to the reviewer that this book falls between two stools—it cannot reproduce the impact of the personality that makes the lecture-demonstration nor is it, on the other hand, the concise summary of disease that is required in a textbook of medicine.

R. E. KELLY.

## SUBARACHNOID HÆMORRHAGE

*Subarachnoid Hœmorrhage.* By JOHN N. WALTON. 1956. Pp. 350 + xv. Edinburgh and London: E. & S. Livingstone Ltd. 30s.

This book provides an exhaustive survey of the clinical, radiological and pathological aspects of subarachnoid hæmorrhage. Symonds remarks in his foreword: "I do not think anything of importance has been omitted," and this certainly seems to be true. Walton has studied 312 cases of spontaneous subarachnoid hæmorrhage admitted to the Royal Victoria Hospital, Newcastle; unfortunately he only saw 30 of these patients during the acute stage, and this fact must limit the value of his observations, especially with regard to treatment. There is a failure, for example, to stress the difficulty of evaluating the various factors which may be operating during the first few days after the hæmorrhage. Admittedly many of his conclusions will be agreed by those with a wider experience.

The bibliography is extensive and up to date. The book is worth its price for this alone.

RONALD HENSON.

XUM

## BRAIN INJURY

*Das Schaedelhirntrauma.* (*Historische, klinische und pathologisch—anatomische Studien an Hand von* 81 *untersuchten Füllen.*) By ERICH KATSENSTEIN. 1956. Pp. 992. Illustrations 592. Basle: Benno Schwabe & Co. £5 19s. 0d.

This publication is based upon 81 case of head injury which the author, a pupil of von Monakow, has investigated from both the clinical and postmortem point of view. The description of the findings alone covers 600 pages. While a systematic study of so large a material is *per se* commendable, much of the space is taken up by almost 600 illustrations many of which are repetitive, or illustrate commonplace detail, or are of poor quality. Moreover some of the interpretations of the histological findings are open to doubt.

The author is at his best when dealing with the historical development and the general discussion of the problems. Here, he displays knowledge and critical understanding of the world literature; his well-balanced list of references covers almost 40 pages. What he has to say about the interplay of factors which determine the lesions is interesting and should be of value to workers in this field. He attaches particular importance to the direction of the mechanical impact and the effect on the colloidal structure of the brain, the disintegration (tixotropie) of which may result in almost instantaneous necrosis and in œdema without intermediary ischæmia and/or anoxia.

A. MEYER.

## NEUROLOGICAL NURSING

*Neurological Nursing.* By JOHN MARSHALL, M.D., M.R.C.P., Senior Lecturer in Neurology, Edinburgh University. 1956. Pp. 181. Oxford: Blackwells. 18s.

Although this useful little book will not directly concern the readers of this journal, they will no doubt wish to bring it to the notice of their nursing colleagues, to whom they can recommend it with every confidence.